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* * * * * * * * * *   Welcome to STN International   * * * * * * * * * *

 NEWS  1            Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2            "Ask CAS" for self-help around the clock
 NEWS  3  FEB 27    New STN AnaVist pricing effective March 1, 2006
 NEWS  4  MAY 10    CA/CAplus enhanced with 1900-1906 U.S. patent records
 NEWS  5  MAY 11    KOREAPAT updates resume
 NEWS  6  MAY 19    Derwent World Patents Index to be reloaded and enhanced
 NEWS  7  MAY 30    IPC 8 Rolled-up Core codes added to CA/CAplus and
                    USPATFULL/USPAT2
 NEWS  8  MAY 30    The F-Term thesaurus is now available in CA/CAplus
 NEWS  9  JUN 02    The first reclassification of IPC codes now complete in
                    INPADOC
 NEWS 10  JUN 26    TULSA/TULSA2 reloaded and enhanced with new search and
                    and display fields
 NEWS 11  JUN 28    Price changes in full-text patent databases EPFULL and PCTFULL
 NEWS 12  JUl 11    CHEMSAFE reloaded and enhanced
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 NEWS 15  AUG 09    INSPEC enhanced with 1898-1968 archive
 NEWS 16  AUG 28    ADISCTI Reloaded and Enhanced
 NEWS 17  AUG 30    CA(SM)/CAplus(SM) Austrian patent law changes
 NEWS 18  SEP 11    CA/CAplus enhanced with more pre-1907 records
 NEWS 19  SEP 21    CA/CAplus fields enhanced with simultaneous left and right
                    truncation
 NEWS 20  SEP 25    CA(SM)/CAplus(SM) display of CA Lexicon enhanced
 NEWS 21  SEP 25    CAS REGISTRY(SM) no longer includes Concord 3D coordinates
 NEWS 22  SEP 25    CAS REGISTRY(SM) updated with amino acid codes for pyrrolysine
 NEWS 23  SEP 28    CEABA-VTB classification code fields reloaded with new
                    classification scheme

 NEWS EXPRESS  JUNE 30 CURRENT WINDOWS VERSION IS V8.01b, CURRENT
               MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 26 JUNE 2006.

 NEWS HOURS    STN Operating Hours Plus Help Desk Availability
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 NEWS IPC8     For general information regarding STN implementation of IPC 8
 NEWS X25      X.25 communication option no longer available

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FILE 'HOME' ENTERED AT 16:51:29 ON 28 SEP 2006

=> file uspatful
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.21       0.21

FILE 'USPATFULL' ENTERED AT 16:51:54 ON 28 SEP 2006
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FILE COVERS 1971 TO PATENT PUBLICATION DATE: 28 Sep 2006 (20060928/PD)
FILE LAST UPDATED: 28 Sep 2006 (20060928/ED)
HIGHEST GRANTED PATENT NUMBER: US7114185
HIGHEST APPLICATION PUBLICATION NUMBER: US2006218687
CA INDEXING IS CURRENT THROUGH 28 Sep 2006 (20060928/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 28 Sep 2006 (20060928/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Jun 2006
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Jun 2006

```
=> e dreyfus p a/in
E1            3     DREYFUS MARC/IN
E2            6     DREYFUS MARC G/IN
E3            0 --> DREYFUS P A/IN
E4            2     DREYFUS PATRICK A/IN
E5            1     DREYFUS ROBERT L/IN
E6            3     DREYFUS ROGER/IN
E7           15     DREYFUS RUSSELL W/IN
E8            2     DREYFUS RUSSELL WARREN/IN
E9            6     DREYFUS THIERRY/IN
E10           4     DREYFUSS DAVID/IN
E11           4     DREYFUSS DAVID D/IN
E12           6     DREYFUSS DAVID DANIEL/IN

=> s e4
L1            2 "DREYFUS PATRICK A"/IN

=> d l1,cbib,clm,1-2

L1   ANSWER 1 OF 2  USPATFULL on STN
2005:56128 Method for the treatment or diagnosis of human pathologies with
    disseminated or difficult to access cells or tissues.
    Dreyfus, Patrick A., Clamart, FRANCE
    Parrish, Elaine, Saint-Denis, FRANCE
    Garcia, Luis, Saint-Denis, FRANCE
    Chokri, Mohamed, Strasbourg, FRANCE
    Bartholeyns, Jacques, Bures-Sur-Yvette, FRANCE
    Peltekian, Elise, Paris, FRANCE
    INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE MEDICALE (I.N.S.E.R.M),
    PARIS CEDEX 13, FRANCE (non-U.S. corporation)I.D.M. IMMUNO-DESIGNED
    MOLECULES, PARIS, FRANCE (non-U.S. corporation)
    US 2005048039 A1 20050303
    APPLICATION: US 2004-766929  A1  20040130 (10)
    DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM    What is claimed is:
       1. A method for preferentially delivering a therapeutic agent or a
       diagnostic agent to a central nervous system (CNS) lesion, comprising
       administering to a patient having or suspected of having a CNS lesion an
       effective amount of exogenous monocyte derived cells, said monocyte
       derived cells being loaded with a therapeutic agent with respect to said
       CNS lesion or a diagnostic marker, and with said monocyte derived cells
       having the properties of mobilisation towards chemotactic factors
       released at or adjacent a CNS lesion, thereby to target cells present in
       the vicinity of said released chemotactic factors.

       2. The method according to claim 1, wherein said monocyte derived cells
       are loaded with a therapeutic agent selected from the group consisting
       of ciliary neurotrophic factor, brain derived neurotrophic factor, glial
       cells derived neurotrophic factor, and tyrosine hydroxylase and DOPA
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carboxylase.

3. The method according to claim 1, wherein the corrective agent is a chemical product.

4. The method according to claim 1, wherein the chemotactic factors are released either by injured or pathological sites spontaneously resulting from said CNS lesion or subsequent to a chemical or physical stimulation of the sites to be treated.

5. The method according to claim 1, wherein the therapeutic agent is selected from the group consisting of ciliary neurotrophic factor, glial cells derived neurotrophic factor, and elements liable to inhibit or to kill abnormally stimulated cells, responsible for or resulting from said CNS lesion.

6. The method of claim 1, wherein said CNS lesion is selected from those causing a disorder selected from the group consisting of adrenoleukodystrophy, spinal muscular atrophy, Gaucher disease, Huntington disease, Alzheimer disease, Parkinson disease, amyotrophic lateral sclerosis, multiple sclerosis, strokes, glioblastoma, cerebral metastasis, infection of the central nervous system, Duchenne disease, Becker disease, muscular dystrophies, neuropathies and muscular necrosis from different origins (including trauma), rheumatoid arthritis, atheromatosis, bone trauma or bone infection or degenerescence, and pulmonary fibrosis.

7. The method of claim 1, wherein said CNS lesion to be treated is selected from those causing a disorder selected from the group consisting of Alzheimer disease, Parkinson disease, amyotrophic lateral sclerosis, multiple sclerosis, and strokes.

L1 ANSWER 2 OF 2 USPATFULL on STN
2002:133199 METHOD FOR THE TREATMENT OR DIAGNOSIS OF HUMAN PATHOLOGIES WITH DISSEMINATED OR DIFFICULT TO ACCESS CELLS OR TISSUES.
DREYFUS, PATRICK A., CLAMART, FRANCE
PARRISH, ELAINE, SAINT-DENIS, FRANCE
GARCIA, LUIS, SAINT-DENIS, FRANCE
CHOKRI, MOHAMED, STRASBOURG, FRANCE
BARTHOLEYNS, JACQUES, BURES-SUR-YVETTE, FRANCE
PELTEKIAN, ELISE, PARIS, FRANCE
US 2002068048 A1 20020606
APPLICATION: US 1997-924830 A1 19970905 (8)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. Method for the treatment or diagnosis of pathologies either expressed in injured or pathological multiple sites in tissues or in the body or expressed in injured or pathological sites of tissues or cells in sites of the body, which are difficult to access, with said sites or areas in immediate proximity to said sites being the source of the release of chemotactic factors for endogenous macrophages, either spontaneously or upon suitable stimulation, wherein said treatment is carried out by administration to the body of an appropriate amount of exogenous monocyte derived cells, said monocyte derived cells being, in the case of treatment, loaded with corrective agents with respect to the pathologies to be treated, and with said monocyte derived cells having the properties of mobilisation towards the source of the above-said released chemotactic factors and to target the cells present in the vicinity of the said released chemotactic factors, and in the case of diagnosis, loaded with a marker enabling the detection of injured or

pathological sites.

2. Method according to claim 1, wherein the treatment with said corrective agents consists in providing deficient elements, such as those responsible for or resulting from the pathology, or providing elements liable to inhibit or to kill abnormally stimulated cells, responsible for or resulting from the pathology.

3. Method according to claim 1 or 2, wherein the corrective agent is a chemical or a biological product such as a polypeptide, a growth factor, a nucleic acid, a gene or the product of a gene.

4. Method according to any of claims 1 to 3, wherein the monocyte derived cells are prepared ex vivo by culturing blood monocytes to obtain monocyte derived cargo cells and in particular mature phagocytes and enhancing their capability (signal linked to the membrane, carrier of product or information, phagocytosis and secretion) or/and loading said phagocytes with appropriate chemical or biological substances or transfecting them with a virus containing an appropriate gene of or with nucleic acids consisting in or containing an appropriate gene.

5. Method according to any of claims 1 to 4, wherein the chemotactic factors are released either by injured or pathological sites spontaneously resulting from the pathology or subsequent to a chemical or physical stimulation of the sites to be treated.

6. Method according to any of claims 1 to 5, wherein the multiple expressed sites result from disseminated cancers or from inflammatory diseases.

7. Method according to any of claims 1 to 5, wherein the injured or pathological sites difficult to access are: the central nervous system, the peripheral nervous and muscular systems and bones.

8. Method according to anyone of claims 1 to 5, wherein the pathologies treated by the method of the present invention include but are not limited to: For the central nervous system Genetic diseases such as: Adrenoleukodystrophy Spinal muscular atrophy Gaucher disease Huntington disease Sporadic diseases such as Alzheimer disease Parkinson disease Amyotrophic lateral sclerosis Multiple sclerosis Strokes Glioblastoma Cerebral metastasis Infection of the central nervous system Peripheral nervous and muscular system Genetic diseases such as: Duchenne disease, Becker disease Muscular dystrophies Non genetic diseases such as: Neuropathies and muscular necrosis from different origins (incl. trauma) Rheumatoid arthritis Atheromatosis Bone trauma or bone infection or degenerescence Pulmonary fibrosis.

9. Monocyte derived cells obtained by culturing blood mononuclear cells to obtain monocytes derived cargo cells, containing a therapeutic agent for a given pathology corresponding to loaded chemical or biological substances such as peptides, polypeptides, proteins and nucleic acids or to virus or nucleic acids which have been transfected into said cells or to these cells loaded externally on the membrane with emitting signals, the said cells having one of more of the following properties: their preparation specifically induce an increased membrane expression level of chemotactic receptors, they are sensitive, particularly in vivo, to chemotactic factors released by sites of call or suffering cells, they have membrane a plasticity such that they can enter difficult injured sites to access such as the central nervous systems, they can rapidly reach sites of call, as soon as two hours to three days, particularly two to three days after systemic injection, they can accumulate into injured sites of call, they remain alive in the vicinity of the injured

or pathological sites for several months, particularly at least up to about 4 months, their morphology becomes similar to the morphology of the cells normally present in the injured sites or pathological and they integrate the tissue cells of the injured or pathological sites, they can release the contained corrective agent in the sites of call, either constitutively or on demand by induction of secretion of said corrective agent.

10. Monocyte derived cells according to claim 9, loaded with chemical or biological substances introduced either by phagocytosis, pinocytosis or physical means such as electropulsation.

11. Monocyte derived cells according to claim 9, transduced using different defective viral vectors such as adenovirus, herpes simplex virus and lentivirus, lentivirus, thereby allowing the transduction of said monocyte derived cells to efficiently introduce therein a cassette containing nucleic sequences coding for a secretable therapeutic peptide, polypeptide or protein under the control of a specific promoter such as Pz.

12. Monocyte derived cells according to claim 9, transfected by introduction of a viral construction consisting of both a murine leukemia provirus (MuLV) containing a gene encoding a peptide, a polypeptide or protein of therapeutic interest and sequences encoding the helper genome allowing its mobilisation and the release of the viral construction at the injured sites.

13. Monocyte derived cells according to claim 12, either transduced sequentially with a) a defective viral vector (matrix vector), able to transduce post-mitotic cells, carrying the sequences encoding entirely the provirus defined in claim 12 (which carries the therapeutic gene), b) a defective viral vector (assembling vector), able to transduce post-mitotic cells, carrying a defective MuLvs gag-pol-env genome for transcomplementation allowing replication of the above-said provirus, or transduced by a single defective viral vector (master vector), able to transduce post-mitotic cells, carrying both the sequences encoding entirely the provirus defined in claim 12 (which carries the therapeutic gene under the control of an internal promoter Py) and a defective MuLvs gag-pol-env genome under the control of an internal promoter Pz, for ciscomplementation allowing replication and production of the above-said provirus.

14. Kit for the preparation of monocyte derived cells according to anyone of claims 9 to 13 comprising: culture means (bags and means) for the maturation of mononuclear cells into phagocytes, particularly macrophages, therapeutic agents to be introduced into the above-said phagocytes and means of introducing them to obtain monocyte derived cells.

15. Kit according to claim 14 containing one or more of the following compnents: means for viral transduction of said phagocytes with defective viral vectors to obtain monocyte derived cells, description of physical (laser, puncture, irradiation . . .) and chemical means to induce the local signal when required, including the time schedule, reagents for the quality control of the viral transduction and of the monocyte derived cells, software for the standard operating procedures and traceability particularly of the following steps: culture of phagocytes, introduction of corrective agents, viral transduction and the recovery of the above-mentioned monocyte derived cells.

16. Pharmaceutical compositions containing as active substance monocytes derived cells according to anyone of claims 9 to 13 in association with

a pharmaceutically acceptable vehicle.

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=> e parrish elaine/in
E1            4      PARRISH DOUGLAS R/IN
E2            1      PARRISH EDWARD W/IN
E3            2 --> PARRISH ELAINE/IN
E4            1      PARRISH ELIZABETH STROUD/IN
E5            1      PARRISH ERNEST H/IN
E6            1      PARRISH EVE J/IN
E7            7      PARRISH FRANK/IN
E8            1      PARRISH FRANK A/IN
E9            1      PARRISH FRANK B/IN
E10           1      PARRISH FRANK W/IN
E11           1      PARRISH FREDERICK C/IN
E12           1      PARRISH FREDERICK W/IN

=> s e3
L2            2 "PARRISH ELAINE"/IN

=> s l2 not l1
L3            0 L2 NOT L1

=> e garcia luis/in
E1            1      GARCIA LUCIANO M/IN
E2            5      GARCIA LUCIO ALFREDO/IN
E3           16 --> GARCIA LUIS/IN
E4            7      GARCIA LUIS A/IN
E5            4      GARCIA LUIS ALEJANDRO REY/IN
E6            1      GARCIA LUIS C/IN
E7            1      GARCIA LUIS M/IN
E8            1      GARCIA LUIS MANUEL/IN
E9            1      GARCIA LUIS MICHELENA/IN
E10          16      GARCIA LUNA ACEVES J J/IN
E11          10      GARCIA LUNA ACEVES J JOAQUIN/IN
E12           2      GARCIA LUNA ACEVES JJ/IN

=> s e3-e5
             16 "GARCIA LUIS"/IN
              7 "GARCIA LUIS A"/IN
              4 "GARCIA LUIS ALEJANDRO REY"/IN
L4           27 ("GARCIA LUIS"/IN OR "GARCIA LUIS A"/IN OR "GARCIA LUIS ALEJANDR
                O REY"/IN)

=> s l4 not l1
L5           25 L4 NOT L1

=> s l5 and (monocyt? or macrophag? or phagocyt?)
         32343 MONOCYT?
         44745 MACROPHAG?
         14575 PHAGOCYT?
L6           0 L5 AND (MONOCYT? OR MACROPHAG? OR PHAGOCYT?)

=> e peltekian elise/in
E1            1      PELTEK SERGEY E/IN
E2            2      PELTEKIAN ARDEM M/IN
E3            3 --> PELTEKIAN ELISE/IN
E4            2      PELTEKOVA VANYA D/IN
E5            1      PELTENBURG WILLEM/IN
E6            3      PELTER ANDREW/IN
E7            1      PELTERS RINE/IN
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E8            5      PELTERS STEPHAN/IN
E9            2      PELTESON FRANK M/IN
E10           1      PELTIE PATRICK/IN
E11           6      PELTIE PHILIPPE/IN
E12           1      PELTIER ARCHIE R/IN

=> s e3
L7            3 "PELTEKIAN ELISE"/IN

=> s l7 not l1
L8            1 L7 NOT L1

=> d l8,ti

L8   ANSWER 1 OF 1  USPATFULL on STN
TI     Canine adenovirus vectors for the transfer of genes in targeted cells


=> d l8,cbib,clm

L8   ANSWER 1 OF 1  USPATFULL on STN
2003:146370 Canine adenovirus vectors for the transfer of genes in targeted
    cells.
    Kremer, Eric, Castelnau le Lez, FRANCE
    Chillon Rodriguez, Miguel, Barcelone, SPAIN
    Soudais, Claire, Fontenay Aux Roses, FRANCE
    Boutin, Sylvie, Alfortville, FRANCE
    Peltekian, Elise, Paris, FRANCE
    Garcia, Luis, Saint Denis, FRANCE
    Vincent, Nathalie, Saintry Sur Seine, FRANCE
    Danos, Olivier, Fontainebleau, FRANCE
    US 2003100116 A1 20030529
    APPLICATION: US 2002-165202  A1  20020607 (10)
    PRIORITY: EP 1999-403061  19991207
    EP 1999-403078  19991208
    DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM    What is claimed is:
       1. Recombinant Canine Adenovirus (CAV) particles obtainable by a process
       comprising the following steps:  a) co-transforming E. coli cells with a
       first plasmid and a pre-transfer plasmid under conditions enabling their
       recombination by homologous recombination, in order to generate a
       transfer plasmid devoid of a functional E1 coding region, comprising the
       desired recombinant vector genome, wherein the first plasmid comprises
       the Inverted Terminal Regions (ITR) and the Packaging Signal (ψ)
       sequences of a CAV genome, and the pretransfer plasmid includes the
       sequence whose insertion in the vector genome is desired, flanked by
       sequences homologous to sequences of the first plasmid surrounding the
       region of the first plasmid where the modification is desired,  b)
       isolating a DNA fragment essentially comprising the recombinant vector
       genome by enzyme restriction,  c) transfecting cells lines that are
       rendered able to transcomplement this recombinant vector genome,  d)
       recovering and purifying the recombinant adenoviral particles produced,
       wherein:  the CAV genome is derived from Canine Adenovirus-2 strain
       Toronto A26/61,  and the cells lines are the Dog Kidney (DK) cell line
       stably expressing the E1 region of the genomic sequence of a CAV-2
       Manhattan strain, deposited at the CNCM on Aug. 16, 1999, under no.
       1-2292 or the DK28Cre cell line deposited at the CNCM under no. 1-2293
       on Aug. 16, 1999.

       2. Canine Adenovirus particles according to claim 1, wherein the CAV
       genome comprises the ITR and packaging signal (ψ) sequences fragment
```

extending from nucleotide 1 to nucleotide 352 of the genomic sequence of the CAV-2Toronto strain.

3. Canine Adenovirus particles according to claim 1, wherein the CAV genome comprises a second packaging signal (ψ) sequence.

4. Canine Adenovirus particles according to claim 3, wherein the ψ sequence is mutated.

5. Canine Adenovirus particles according to claim 1, wherein the expression cassette contains a nucleotide sequence to be transferred whose expression is driven by a promoter selected from the group consisting of a viral promoter, a non viral promoter and a cellular promoter.

6. Canine Adenovirus particles according to claim 1, wherein the expression cassette is substituted for the E1 coding region of the CAV genome.

7. Canine Adenovirus particles according to claim 1, wherein the CAV-2 Toronto strain A26/61 genomic sequence is deleted from nucleotide 412 to nucleotide 2897.

8. Canine Adenovirus particles according to claim 1, which contains mammalian stuffer sequences.

9. A CAV vector genome such as comprised in particles according to claim 1.

10. A DNA construct comprising the CAV vector genome according to claim 9.

11. A plasmid comprising the CAV genome according to claim 9, selected from the group consisting of pEJK25, p25GFP, pCAVGFP, and pCAVBFP.

12. A transcomplementing cell line for the production of Canine Adenovirus vector particles, which is a Dog Kidney (DK) cell line stably expressing the E1 region of the genomic sequence of a CAV-2 Manhattan strain, deposited at the CNCM on Aug. 16, 1999, under no. 1-2292.

13. A transcomplementing cell line according to claim 12 wherein the selection genes encoding for Neomycin and Zeocin resistance are substituted by other marker genes.

14. A transcomplementing cell line according to claim 12, which further expresses a Cre recombinase.

15. A transcomplementing cell line according to claim 14, which is the DK28Cre cell line deposited at the CNCM under no. 1-2293 on Aug. 16, 1999.

16. A transcomplementing cell line according to claim 12 wherein said cell line is transfected with the CAV genome of claim 9.

17. Use of the transcomplementing cell line according to claim 12 for the production of CAV vector particles.

18. Use of Canine Adenovirus particles according to claim 1 for the preparation of a therapeutic composition for the treatment or modification of neuronal cells.

19. Use of Canine Adenovirus particles according to claim 1, for the

preparation of a therapeutic composition, for the targeted administration of a nucleotide sequence of therapeutic interest, in neuronal cells.

20. Use of Canine Adenovirus particles according to claim 1 for the preparation of a therapeutic composition capable of specifically interacting with neuritic terminations.

21. Use of Canine Adenovirus particles according to claim 1 for the preparation of a therapeutic composition for the transfer of a nucleotide sequence of interest in vivo in neuronal cells.

22. Use of a Canine Adenovirus particles according to claim 1, for the preparation of a therapeutic composition for the treatment of a human patient presenting a humoral immunity against human adenovirus.

23. Use of Canine Adenovirus particles according to claim 1 for the screening of the delivery of a nucleotide sequence of interest in neuronal cells.

24. Recombinant Adenovirus particles according to claim 1 wherein the canine adenoviral genome is deleted of essentially all viral coding sequences and the transcomplementing cells are transfected by a helper virus devoid of E1.

25. A kit for the generation of recombinant CAV particles according to claim 1, comprising: a) transcomplementation cells, b) a first plasmid, devoid of the E1 coding region of the CAV genome, c) a pre-transfer plasmid, including sequences homologous to sequences of the first plasmid flanking the E1 deletion, d) E. coli cells.

26. A kit for the generation of recombinant CAV particles according to claim 25, comprising: a) transcomplementation cells, b) a first plasmid, devoid of all the viral coding sequences of the CAV genome, c) a pre-transfer plasmid, including sequences homologous to sequences of the first plasmid, e) E. coli cells.

```
=> d l4,ti,1-10

L4   ANSWER 1 OF 27  USPATFULL on STN
TI     Facility access control system including temporary personnel
       identification badges with expiration indicia

L4   ANSWER 2 OF 27  USPATFULL on STN
TI     Medical facility employee scheduling method using patient acuity
       information

L4   ANSWER 3 OF 27  USPATFULL on STN
TI     Report generation and distribution system and method for a time and
       attendance recording system

L4   ANSWER 4 OF 27  USPATFULL on STN
TI     Apparatus and method for heating and cooling an article

L4   ANSWER 5 OF 27  USPATFULL on STN
TI     Method for the treatment or diagnosis of human pathologies with
       disseminated or difficult to access cells or tissues

L4   ANSWER 6 OF 27  USPATFULL on STN
TI     Automated labor overtime projection method
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L4   ANSWER 7 OF 27  USPATFULL on STN
TI     Method and system for deterministic control of an emulation

L4   ANSWER 8 OF 27  USPATFULL on STN
TI     Method and system for deterministic control of an emulation

L4   ANSWER 9 OF 27  USPATFULL on STN
TI     Method and system for deterministic control of an emulation

L4   ANSWER 10 OF 27  USPATFULL on STN
TI     Canine adenovirus vectors for the transfer of genes in targeted cells


=> e bartholeyns jacque/in
E1            1     BARTHOLET THOMAS G/IN
E2            1     BARTHOLET WILLIAM/IN
E3            0 --> BARTHOLEYNS JACQUE/IN
E4           23     BARTHOLEYNS JACQUES/IN
E5            1     BARTHOLF HEATHER A/IN
E6            4     BARTHOLF JOEL/IN
E7            1     BARTHOLF PAUL/IN
E8            1     BARTHOLF THOMAS/IN
E9           39     BARTHOLIC DAVID B/IN
E10           1     BARTHOLIN HENRIK/IN
E11           1     BARTHOLIN MICHEL/IN
E12           2     BARTHOLIN NIELS/IN

=> s e4
L9           23 "BARTHOLEYNS JACQUES"/IN

=> s l9 not l1
L10          21 L9 NOT L1

=> d l10,ti,1-5

L10  ANSWER 1 OF 21  USPATFULL on STN
TI     Process of cell electrofusion

L10  ANSWER 2 OF 21  USPATFULL on STN
TI     Humanized biomaterials, a process for their preparation and their
       applications

L10  ANSWER 3 OF 21  USPATFULL on STN
TI     Macrophages, process for preparing the same and their use as active
       substances of pharmaceutical compositions

L10  ANSWER 4 OF 21  USPATFULL on STN
TI     Cell compositions containing macrophages, presenting anti-infectious and
       hematopoietic properties

L10  ANSWER 5 OF 21  USPATFULL on STN
TI     Dehydrated antigen presenting cells usable for vaccination


=> d l10,cbib,clm,1-21

L10  ANSWER 1 OF 21  USPATFULL on STN
2006:80502 Process of cell electrofusion.
    Tessie, Justin, Agne, FRANCE
    Bartholeyns, Jacques, Turquant, FRANCE
    US 2006068495 A1 20060330
```

APPLICATION: US 2003-504939 A1 20030221 (10)
WO 2003-EP1798 20030221 20050516 PCT 371 date
PRIORITY: EP 2002-290437 20020222
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. (canceled)

2. A method for production of a cell population enriched in C1-C2 heterohybrids comprising a step of applying an electrical field to a mixture containing a first type of cell (C1), a second type of cell (C2), a bispecific ligand able to bind to C1 and/or to C2 and non-covalent complexes formed between C1, C2 and the bispecific ligand, said electrical field, being designed to induce cellular fusion, enabling formation of heterohybrids.

3. The method according to claim 2 comprising a preliminary step of preincubation of C1, C2 and the bispecific ligand for a time sufficient for the formation of non-covalent complexes between C1, C2 and the ligand.

4. The method according to claim 2, said method comprising the step of applying to C1 and/or to C2 a treatment intended to kill or to block proliferation of the cells, before preincubation of C1, C2 and the bispecific ligand

5. The method according to claim 2, said method comprising the step of applying to C1-C2 heterohybrids a treatment intended to kill or to block proliferation of the hybrids after the applying of the electrical field designed to induce cellular fusion.

6. The method according to claim 2, characterized in that said mixture to which an electrical field is applied is in a form of a sequential flow.

7. The method according to claim 6, characterized in that it comprises steps of adjusting intensity of said electrical field, adjusting number, and duration of pulse(s) of the said electrical field.

8. The method according to any one of claims 2 to 5, characterized in that said mixture to which an electrical field is applied is in a form of a continuous flow.

9. The method according to claim 8 characterized in that it comprises steps of adjusting speed of said continuous flow, intensity of said electrical field, adjusting number, duration and frequency of pulse(s) of the said electrical field in order to deliver a given number of electrical field pulses on the mixture.

10. The method according to claim 8 characterized in that the electrical field is applied to the mixture in a direction approximately parallel or approximately perpendicular to the flow, and preferably approximately parallel to the flow.

11. The method according to claim 9 characterized in that the step of adjusting said speed of the said continuous flow allows further to a complex formed between C1, bispecific ligand and C2 to have its greatest axis parallel to said electrical field.

12. The method according to claim 9 characterized in that said speed of said continuous flow inside said electrical field is adjusted in order to stay preferably in laminar regime.

13. The method according to claim 2 characterized in that intensity of said electrical field is comprised from about 100 to about 4000 V/cm.

14. The method according to claim 2 characterized in that duration of said electrical field is comprised from about 1 microsecond to about 100 millisecond.

15. The method according to claim 2 characterized in that number of electrical impulses applied to said mixture is comprised from about 1 to 100, and preferably from about 4 to 20.

16. The method according to claim 2 characterized in that C1, C2 and the mixture are contained in a medium having an osmolarity comprised from about 150 to about 400 mOSm/kg, more preferably from about 200 to about 400 mOsm/kg, and more preferably about 200 mOsm/kg.

17. The method according to claim 2 characterized in that the electrical impulse is unipolar or bipolar.

18. The method according to claim 2 characterized in that the shape of the electrical impulse is a square wave, a sinusoid, a triangle, or with exponential decline.

19. The method according to claim 2 characterized in that said mixture is left, after being submitted to said electrical field, at rest a time sufficient to allow formation of hybrids, said sufficient time ranging from about 30 minutes to about 4 hours, preferably about 1 hours.

20. The method according to claim 2 characterized in that the first type of cell is an antigen presenting cell, and preferably a dendritic cell or a macrophage.

21. The method according to claim 2 characterized in that the first type of cell is a monocyte-derived antigen presenting cell.

22. The method according to claim 2 characterized in that the second type of cell is a tumor cell, either alive or treated so as to be killed or detoxified.

23. The method according to claim 2 characterized in that the bispecific ligand is an antibody or a bispecific antibody.

24. The method according to claim 22 characterized in that the bispecific ligand binds to said antigen presenting cell via high affinity Fc receptors, for one part, and to said tumor cell via a cell surface antigen, for the other part.

25. A method for the production of C1-C2 heterohybrids formed between a first type of cells (C1), a second type of cells (C2) and a bispecific ligand able to bind to C1 and/or to C2 comprising a step of preparation of a cell population enriched in C1-C2 heterohybrids, according to claim 2, and subsequent isolation of C1-C2 heterohybrids.

26. A cell population enriched in C1-C2 heterohybrids such as obtained by applying a method according to claim 2, characterized in that it contains from about 60 to about 100% of living cells.

27. A cell population enriched in C1-C2 heterohybrids comprising a percentage of heterohybrids from about 15 to about 80% of cells.

28. A device for implementing a method for the production of a cell

population enriched in heterohybrids according to claim 2 characterized in that it comprises at least one pulsing chamber (2) comprising at least two electrodes adapted to produce a substantially uniform field transverse to the flow passing between them, said electrodes being plate (15, 16) or bar (18, 19) disposed substantially parallel to each other in a plane substantially parallel to the flow traversing between the electrodes.

29. A device for reduction to practice of a method for the production of a cell population enriched in heterohybrids according to claim 2 characterized in that it comprises at least one pulsing chamber (2) comprising at least two electrodes adapted to produce a substantially uniform field approximately parallel to the flow passing between them, said electrodes being in form of a grid (23, 24), a perforated disc or a ring (20, 21).

30. The device according to claim 29 characterized in that inner edges of said electrodes being ring-shaped (20, 21) are rounded.

31. The device according to claim 29 characterized in that a ratio of the length of pulsing chamber to the inner diameter of said ring-shaped electrodes is greater than about 2.5, more preferably is in a range from about 2.5 to about 10, and more preferably is substantially equal to about 3

32. The device according to claim 28 characterized in that it comprises in addition to at least one pulsing chamber (2), a mixing chamber (1), an incubation chamber (3), feeding means (4, 5, 6, 10a) for feeding liquid partners of mixture into said mixing chamber (1), first connection means (7) for liquid communication between an outlet of said mixing chamber (1) and an inlet of said pulsing chamber (2), and second connection means (8) for liquid communication between an outlet of said pulsing chamber (2) and an inlet of said incubation chamber (3).

33. The device according to claim 32 characterized in that said feeding means comprise means for purging liquid, such as a syringe or a pipe connected to a peristaltic pump (10a).

34. The device according to claim 33 characterized in that at least one of the first (7) and second (8) connection means are equipped with closure means such as a tap (13, 14) or a clamp, allowing their closure once said pulsing chamber (2) is filled, and said second mean being connected with a peristaltic pump (10b).

35. The device according to claim 28 characterized in that it comprises at least two said pulsing chambers being mounted in parallel.

36. A kit for the production of a cell population enriched in C1-C2 heterohybrids, said kit comprising fusion chamber, bags, connecting tubes and chambers in plastic and/or plastic and metal, media, washing solutions and a device allowing the flow of the mixture.

37. A pharmaceutical composition comprising at least, in association with a pharmaceutically acceptable vehicle, a cell population according to claim 26.

38. (canceled)

39. A method for preparing a pharmaceutical, comprising adding a cell population according to claim 26 to a pharmaceutically acceptable vehicle.

L10 ANSWER 2 OF 21 USPATFULL on STN
2005:95001 Humanized biomaterials, a process for their preparation and their applications.
Bartholeyns, Jacques, Turquant, FRANCE
I.D.M. Immuno-Designed Molecules, Paris, FRANCE (non-U.S. corporation)
US 6881413 B1 20050419
WO 2001015753 20010308
APPLICATION: US 2002-69575 20000822 (10)
WO 2000-EP8157 20000822 20000612 PCT 371 date
PRIORITY: EP 1999-402149 19990830
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A humanized biomaterial ready for implantation comprising a porous bio-compatible composite material that is customized and implanted with living monocyte derived cells substantially irreversibly bound to said porous biocompatible composite material, wherein said monocyte derived cells are macrophages which have been obtained by ex vivo differentiation of blood monocytes taken from a human patient and wherein the living macrophages are cultured under conditions such that when implanted into the porous biocompatible composite material the macrophages penetrate and substantially irreversibly bind to said porous biocompatible composite material.

2. The humanized biomaterial according to claim 1, wherein the biocompatible composite material is selected from the group consisting of microfibers, ceramic materials, metal oxides, calcium phosphate ceramic, glass fibers, carbon fibers, hydroxylapatite, silicon carbide, silicon nitride, collagen polymers and a mixture of these different materials.

3. The humanized biomaterial according to claim 2, wherein said biocompatible material is aluminum oxide.

4. An implant comprising the humanized biomaterial according to claim 1, and wherein said implant is structured in a form selected from the group consisting of scaffold, tissue-supporting sponges, bone and cartilage.

L10 ANSWER 3 OF 21 USPATFULL on STN
2004:294590 Macrophages, process for preparing the same and their use as active substances of pharmaceutical compositions.
Chokri, Mohamed, Deuil-la-Barre, FRANCE
Bartholeyns, Jacques, Bures-sur-Yvette, FRANCE
I.D.M. Immuno-Designed Molecules, Paris, FRANCE (non-U.S. corporation)
US 6821516 B1 20041123
APPLICATION: US 1999-304564 19990504 (9)
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A method for treating cancer, comprising administering to a patient in need of said treatment (i) macrophages having at least one of the following properties: their cytotoxic activity without IFN-γ is increased by about 20 to 30% with respect to standard macrophages; their cytotoxic activity with IFN-γ is increased by about 20 to about 40% with respect to standard macrophages incubated with IFN-γ; deactivation of the cytotoxic activity following activation of IFN-γ is such that sixty hours after activation with IFN-γ, the residual cytotoxic activity is at least 30% of the maximum cytotoxic activity presented by the macrophages due to IFN-γ activation, with said cytotoxic activity being measured as a percentage of the

inhibition of 3-H thymidine incorporation by target tumoral cells, particularly U 937 cells; and (ii) bispecific antibodies which recognize both a) an antigen of said macrophages, and b) an antigen of a tumoral cell to be targeted by said macrophages.

2. The method according to claim 1, wherein the macrophages are injected at the same time as the bispecific antibodies.

3. The method according to claim 1, wherein the bispecific antibodies are preincubated with macrophages before injection.

L10 ANSWER 4 OF 21 USPATFULL on STN
2004:122958 Cell compositions containing macrophages, presenting anti-infectious and hematopoietic properties.
Klein, Bernard, Saint-Clement-de-Riviere, FRANCE
Lu, Zhao Yang, Castelnau-le-Lez, FRANCE
Bartholeyns, Jacques, Turquant, FRANCE
I.D.M. Immuno-Designed Molecules, Paris, FRANCE (non-U.S. corporation)Centre Hospitalier Universitaire de Montpellier, Montpellier Cedex, FRANCE (non-U.S. corporation)
US 6737051 B1 20040518
WO 2000045827 20000810
APPLICATION: US 2001-890652 20011127 (9)
WO 2000-EP647 20000127
PRIORITY: EP 1999-400239 19990203
DOCUMENT TYPE: Utility; GRANTED.
CLM What is claimed is:

1. A cell composition, comprising: macrophages present in an amount of about 10 to about 70%, said percentage is expressed with respect to the total number of cells; and progenitor cells present in an amount of at least 0.1%, said percentage being expressed with respect to the total number of cells.

2. The cell composition according to claim 1, wherein said progenitor cells are present in an amount of about 0.1 to about 20%, said percentage being expressed with respect to the total number of cells.

3. The cell composition according to claim 1, further comprising myeloid cells, said myeloid cells are present in an amount of about 10% to about 30%, said percentage being expressed with respect to the total number of cells.

4. The cell composition according to claim 1, wherein said progenitor cells contain from about 0.1 to about 20% of stem cells, expressed with respect to the total number of progenitor cells.

5. A composition comprising, a pharmaceutically acceptable carrier and as an active substance, the cell composition according to claim 1.

6. The cell composition according to claim 1, wherein said composition is derived from a peripheral blood mononuclear cell composition containing: from about 10 to about 50% of monocytes, from about 10 to about 70% of lymphocytes, from about 0.1 to about 20% of progenitor cells, from about 1 to about 50% of polynuclear cells, and from about 0.1 to about 20% of stem cells.

7. A cell composition comprising macrophages, myeloid cells and progenitor cells, said progenitor cells are present in an amount of about 0.1% to about 20%, said macrophages are in an amount of about 10 to about 70%, and said percentages are expressed with respect to the total number of cells, as obtained by a process comprising the following

steps: collecting mononuclear cells and progenitors by apheresis co-culturing blood mononuclear cells and progenitors, after washing of platelets, granulocytes and erythrocytes, for 4 to 10 days, in a medium allowing differentiation of monocytes into macrophages and myeloid progenitors into polynuclear cells.

8. A cell composition comprising macrophages, myeloid cells and progenitor cells, wherein said progenitor cells are present in an amount of about 0.1% to about 20%, said macrophages being in an amount of about 10 to about 70%, said percentages are expressed with respect to the total number of cells, as obtained by a process comprising the following steps: mobilizing progenitor cells in the blood of a patient by premedication of said patient with G-CSF and/or GM-CSF or G-CSF and cyclophosphamide, collecting mononuclear cells and progenitors by apheresis, co-culturing of the blood mononuclear cells and progenitors, after washing of platelets, granulocytes and erythrocytes, for 4 to 10 days, in a medium allowing differentiation of monocytes into macrophages and myeloid progenitors into polynuclear cells.

9. A composition comprising, a pharmaceutically acceptable carrier and as an active substance, the cell composition according to claim 2.

10. A composition comprising, a pharmaceutically acceptable carrier and as an active substance, the cell composition according to claim 3.

11. A composition comprising, a pharmaceutically acceptable carrier and as an active substance, the cell composition according to claim 4.

12. The cell composition according to claim 2, wherein said composition is derived from a peripheral blood mononuclear cell composition containing: from about 10 to about 50% of monocytes, from about 10 to about 70% of lymphocytes, from about 0.1 to about 20% of progenitor cells, from about 1 to about 50% of polynuclear cells, and from about 0.1 to about 20% of stem cells.

13. The cell composition according to claim 3, wherein said composition is derived from a peripheral blood mononuclear cell composition containing: from about 10 to about 50% of monocytes, from about 10 to about 70% of lymphocytes, from about 0.1 to about 20% of progenitor cells, from about 1 to about 50% of polynuclear cells, and from about 0.1 to about 20% of stem cells.

14. The cell composition according to claim 4, wherein said composition is derived from a peripheral blood mononuclear cell composition containing: from about 10 to about 50% of monocytes, from about 10 to about 70% of lymphocytes, from about 0.1 to about 20% of progenitor cells, from about 1 to about 50% of polynuclear cells, and from about 0.1 to about 20% of stem cells.

15. The cell composition according to claim 7, wherein said medium contains at least one component selected from the group consisting of cytokines and growth factors.

16. The cell composition according to claim 8, wherein said medium contains at least one component selected from the group consisting of cytokines and growth factors.

L10 ANSWER 5 OF 21 USPATFULL on STN
2004:94688 Dehydrated antigen presenting cells usable for vaccination.
Bartholeyns, Jacques, Paris, FRANCE
Prigent, Didier, Bures sur Yvette, FRANCE

US 2004072140 A1 20040415
APPLICATION: US 2003-433960 A1 20031118 (10)
WO 2001-EP13354 20011119
PRIORITY: EP 2000-403429 20001207
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. Dehydrated antigen presenting cells obtained from initial fresh antigen presenting cells and being liable to generate an immune response against the same antigen(s) as the one(s) against which the initial antigen presenting cells are directed.

2. Dehydrated antigen presenting cells according to claim 1 characterized in that they present on their surface MHC class I and MHC class II molecules, with CD16, CD64 and CD45 molecules.

3. Dehydrated antigen presenting cells according to claim 1 characterized in that they present on their surface MHC class I and MHC class II molecules, with CD40, CD80 and CD86 co-stimulatory molecules.

4. Dehydrated antigen presenting cells according to any one of claims 1 or 3 characterized in that cells have been loaded with at least one antigen prior being dehydrated.

5. Dehydrated antigen presenting cells according to any one of claims 1 to 4 characterized in that they present previously interiorised or adsorbed antigenic peptides on their surface, in association with MHC class I and/or MHC class II molecules.

6. Dehydrated antigen presenting cells according to any one of claims 1 to 5 characterized that they are blood cells, cells derived from blood cells, or blood stem cells or somatic cells.

7. Dehydrated antigen presenting cells according to claim 6 chosen within the group consisting of monocyte derived cells, macrophages and dendritic cells.

8. Dehydrated antigen presenting cells according to any one of claims 1 to 7 characterized in that cells result from the fusion of antigen presenting cells and tumoral cells.

9. Dehydrated antigen presenting cells according to any one of claims 1 or 2 characterized in that they are dehydrated macrophages which have preserved capacity of fresh macrophages to bind to specific cells, tissues or antigens, in vitro or in vivo, and to deliver to this site an agent which may have a therapeutic effect.

10. Method of preparation of dehydrated antigen presenting cells obtained from initial fresh antigen presenting cells and being liable to generate an immune response against the same antigen(s) as the one(s) against which the initial antigen presenting cells are directed comprising the following step: sublimation of ice contained in a frozen cellular preparation of fresh antigen presenting cells under low pressure conditions.

11. Method of preparation of dehydrated antigen presenting cells according to claim 10, in which the freezing of the cells is achieved under the conjugated action of low temperature and low pressure conditions.

12. Dehydrated antigen presenting cells liable to be obtained according to the process of any one of claims 10 or 11.

13. Rehydrated antigen presenting cells obtained from the rehydration of dehydrated antigen presenting cells according to any one of claims 1 to 9.

14. Method of preparation of rehydrated antigen presenting cells according to claim 13 comprising the addition of a resuspension solution to dehydrated cells according to any claim 1 to 9, the dehydrated antigen presenting cells and the resuspension solution being at about the same temperature.

15. Pharmaceutical compositions containing as active substance dehydrated antigen presenting cells, according to claim 1 to 9 or rehydrated antigen presenting cells according to claim 13.

16. Cellular vaccine compositions containing as active substance dehydrated antigen presenting cells, according to claim 1 to 9, or rehydrated antigen presenting cells according to claim 13.

L10 ANSWER 6 OF 21 USPATFULL on STN
2004:78837 Combined preparation for the treatment of neoplasic diseases or of infectious diseases.
Bartholeyns, Jacques, Bures-sur-Yvette, FRANCE
Fouron, Yves, Marlborough, MA, United States
Romet-Lemonne, Jean-Loup, Paris, FRANCE
I.D.M. Immuno-Designed Molecules, Paris, FRANCE (non-U.S. corporation)
US 6713056 B1 20040330
WO 9951248 19991014
APPLICATION: US 2000-647529 20001129 (9)
WO 1999-EP2105 19990329
PRIORITY: EP 1998-400783 19980402
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. Preparation comprising the following individual components, in the form of a kit: monocyte derived cells which have been in culture for 5 to 10 days, and chemotherapy drugs, for the simultaneous, separate or sequential use, for the treatment of cancer or infectious diseases in a patient.

2. Preparation according to claim 1, wherein the monocyte derived cells are prepared according to the method comprising the following steps: 1) recovering blood derived mononuclear cells directly from blood apheresis or from blood bag collection, followed if necessary by centrifugation, to eliminate the red blood cells granulocytes and platelets, and collection of peripheral blood leukocytes; 2) washing peripheral blood leukocytes obtained at the preceding steps by centrifugation (to remove 90% of platelets, red blood cells and debris) to obtain mononuclear cells; 3) resuspending the total mononuclear cells (monocytes+lymphocytes) obtained at the preceding step in culture medium (RPMI or IMDM type) at 106 to 2.107 cells/ml, completed by at least one of cytokines and autologous serum, and culture at 37° C. under O2/CO2 atmosphere in hydrophobic gas permeable bags, to obtain monocyte derived cells and contaminating lymphocytes.

3. Preparation according to claim 1, wherein the chemotherapy drug is selected from the group of compounds consisting of anthracyclins, daunorubicin, adriamycin, taxoter derivatives, vinca alcaloids, vincristine, taxol, carmustine, cisplatin, fluorouracils, polyamine inhibitors, topoisomerase inhibitors, tamoxifene, prodasone, sandostatine, sodium butyrate, mitomycin C, penicillins,

β-lactamines, cephalosporines, cyclines, aminoglucosides, macrolides, sulfamides, AZT, protease inhibitors, acyclovir, retrovir and foscarnet.

4. Preparation according to claim 1, wherein the monocyte derived cells and the chemotherapy drugs are in the form of injectable solutions.

5. Preparation according to claim 4, wherein the form of injectable solutions are for locally injectable solutions.

6. Preparation according to claim 4, wherein the form of injectable solutions permit systemically injectable solutions.

7. A process for preparing monocyte derived cells and chemotherapy drugs in the form of a kit for simultaneous, separate, or sequential use for the treatment of cancer or infectious diseases in a patient, comprising the following steps: 1) recovering blood derived mononuclear cells directly from blood apheresis or from blood bag collection, followed if necessary by centrifugation, to eliminate the red blood cells granulocytes and platelets, and collection of peripheral blood leukocytes; 2) washing peripheral blood leukocytes obtained at the preceding steps by centrifugation (to remove 90% of platelets, red blood cells and debris) to obtain mononuclear cells; 3) resuspending the total mononuclear cells (monocytes+lymphocytes) obtained at the preceding step in culture medium (RPMI or IMDM type) at 106 to 2.107 cells/ml, completed by at least one of cytokines and autologous serum, and culture at 37° C. under O2/CO2 atmosphere in hydrophobic gas permeable bags, to obtain monocyte derived cells and contaminating lymphocytes; and 4) assembling said monocvte derived cells in a kit with chemotherapy drugs.

8. The process according to claim 7, further comprising centrifuging said monocyte derived cells, washing, and resuspending said monocyte derived cells to obtain a suspension of the monocyte derived cells.

9. The process according to claim 8, further comprising the additional step of freezing said suspension at a temperature below or equal to -80° C. aliquots with the addition of a cryopreservative.

10. The process according to claim 9, further comprising melting said frozen aliquots to obtain a suspension of monocyte derived cells, washing said suspension, and resuspending said suspension in an isotonic medium to obtain a suspension of monocyte derived cells.

11. Process for the simultaneous, separate, or sequential use of a preparation for the treatment of cancer or infectious diseases in a patient, comprising: administering to said patient an effective amount of said preparation, wherein said preparation comprises the following individual components, in the form of a kit: monocyte derived cells which have been in culture for 5-10 days, and chemotherapy drugs.

12. The process according to claim 11, wherein the monocyte derived cells are administered at a dose from 107 to 1010 monocyte derived cells per injection.

13. The process according to claim 12, wherein the monocyte derived cells are administered at a dose from 108 to 109.

14. The process according to claim 12, wherein the monocyte derived cells are administered repeatedly up to ten times, the interval between each administration being between three days to two months.

15. The process according to claim 11, wherein the chemotherapy drug is administered at a dose of 0.1 to 1000 mg/day.

16. The process according to claim 11, wherein in the case of administration of a drug, said drug is selected from the group consisting of cytotoxic compounds, cytostatic compounds, compounds inducing apoptosis or cytokines, said drug administered at a dose of 0.1 to 100 mg/day.

17. The process according to claim 11, wherein the chemotherapy drug is administered repeatedly up to 10 times, the interval between each administration being between one day to two months.

18. The process according to claim 11, wherein the chemotherapy drug and the monocyte derived cells are injected simultaneously.

19. The process according to claim 11, wherein the chemotherapy drug and the monocyte derived cells are administered sequentially, the chemotherapy drug being administered before the monocyte derived cells.

20. The process according to claim 19, wherein the interval of time between the administration of the monocyte derived cells and the administration of the chemotherapy drugs is of one day to two months.

21. The process according to claim 11, wherein the monocyte derived cells and the chemotherapy drug are administered sequentially, the monocyte derived cells being administered before the chemotherapy drug.

22. The process according to claim 11, wherein the monocyte derived cells are administered before the administration of a vaccine directed to tumor or infectious antigens, the monocyte derived cells administration being preceded by a chemotherapy treatment.

23. The process according to claim 22, wherein the interval of time between the administration of the chemotherapy drug and the administration of the monocyte derived cells is one day to two months.

24. The process according to claim 19, wherein the administration of monocyte derived cells is followed by an administration of the chemotherapy drug.

25. The process according to claim 24, wherein the interval of time between the administration of monocyte derived cells and the administration of chemotherapy drugs is one day to two months.

L10 ANSWER 7 OF 21 USPATFULL on STN
2004:59770 Apoptotic bodies, monocyte derived cells containing the same, a process for their preparation and their uses as vaccines.
Gregoire, Marc, Nantes, FRANCE
Bartholeyns, Jacques, Bures-sur-Yvette, FRANCE
INSERM Institut National de la Sante et de la Recherche Medicale, Paris Cedex, FRANCE (non-U.S. corporation) IDM Immuno -Design Molecules, Paris, FRANCE (non-U.S. corporation)
US 6703016 B1 20040309
WO 9958645 19991118
APPLICATION: US 2000-700108 20001228 (9)
WO 1999-EP3136 19990506
PRIORITY: EP 1998-401123 19980511
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A human monocyte derived cell having an integrated apoptotic body, comprising: an apoptotic body which is obtained from human tumor biopsy and induced to apoptosis, wherein said apoptotic body when introduced into said monocyte derived cell has plasma membrane integrity, contains intact mitochondria and cleaved nuclear DNA originating from said tumor cells, presents unmasked tumor antigens, presents MHC antigens from said patient and is a vesicle above 0.1 μm, and wherein said human monocyte derived cell is stimulated by thermal stress, pressure change, microwaves, electric shock or electropulsation, it presents membrane tumor specific antigens and unmasked antigens which are not present on said human monocyte derived cell before integration of the apoptotic body, and further presents the patient's MHC and costimulatory molecules in a conformation allowing induction of an immunostimulatory response.

2. A human monocyte derived cell having an integrated apoptotic body, produced by the process comprising: culturing human monocyte derived cells and apoptotic bodies to enable phagocytosis of said apoptotic bodies by said monocyte derived cells, wherein said apoptotic bodies are obtained from human tumor cells recovered from a patient's tumor biopsy and induced to apoptosis, said apoptotic bodies maintain plasma membrane integrity, contains intact mitochondria and cleaved nuclear DNA originating from said tumor cells, present unmasked tumor antigen, presents MHC antigens from said patient and are vesicles above 0.1 μm, incubating said monocyte derived cells containing apoptotic bodies to enable intracellular digestion of apoptotic bodies and presentation of tumor and unmasked antigens on the monocyte derived cell membrane in a conformation allowing induction of an immunostimulatory response, and stimulating said monocyte derived cells by thermal stress, pressure change, microwaves, electric shock or electropulsation.

3. The human monocyte derived cell having an integrated apoptotic body according to claim 2, wherein said process further comprises: centrifuging said monocyte derived cells containing apoptotic bodies at a temperature enabling cell preservation, and resuspending said monocyte derived cells containing apoptotic bodies in an isotonic medium containing autologous serum.

4. The human monocyte derived cell having an integrated apoptotic body according to claim 2, wherein said process further comprises: centrifuging the monocyte derived cells containing apoptotic bodies at a temperature enabling cell preservation, resuspending said monocyte derived cells containing apoptotic bodies, and storing said monocyte derived cells containing apoptotic bodies at a temperature below about 10° C.

5. The human monocyte derived cell having an integrated apoptotic body according to claim 2, wherein said process further comprises: centrifuging the monocyte derived cells containing apoptotic bodies at a temperature enabling cell preservation, resuspending said monocyte derived cells containing apoptotic bodies, and freezing aliquots of stimulated monocyte derived cells containing apoptotic bodies with a cryopreservative.

6. The human monocyte derived cell having an integrated apoptotic body according to claim 2, wherein said process further comprises: preparing said monocyte derived cells by recovering blood derived mononuclear cells directly from blood apheresis or from blood bag collection, followed optionally by centrifugation to collect peripheral blood leukocytes and to eliminate a substantial part of red blood cells, granulocytes and platelets, washing said peripheral blood leukocytes to obtain mononuclear cells, resuspending said monocyte derived cells and leukocytes in a culture medium at 106 to 2x107 cells/ml,

culturing said monocyte derived cells and leukocytes for 5 to 10 days at 37° C. under O2/CO2 atmospehere in hydrophobic gas permeable bags to obtain immunostimulatory monocyte derived cells and contaminating lymphocytes, and optionally integrating a DNA coding for a protein of interest.

L10 ANSWER 8 OF 21 USPATFULL on STN

2004:24347 Combined preparation for the treatment of neoplasic diseases or of infectious diseases.

Bartholeyns, Jacques, Bures-Sur-Yvette, FRANCE
Fouron, Yves, Marlborough, MA, UNITED STATES
Romet-Lemonne, Jean-Loup, Paris, FRANCE
I.D.M. IMMUNO-DESIGNED MOLECULES, PARIS, FRANCE (non-U.S. corporation)

US 2004018184 A1 20040129
APPLICATION: US 2003-622727 A1 20030721 (10)
PRIORITY: EP 1998-400783 19980402
DOCUMENT TYPE: Utility; APPLICATION.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

CLM What is claimed is:

1. A method for treating a patient suffering from a neoplasic or infectious disease, comprising: administering an effective amount of monocyte derived cells and an effective amount of chemotherapy drugs to said patient.

2. The method according to claim 1, wherein said monocyte derived cells and chemotherapy drugs are administered simultaneously.

3. The method according to claim 1, wherein the chemotherapy drug is selected from the group consisting of anthracyclins, daunorubicin, adriamycin, taxoter derivatives, vinca alcaloids, vincristine, taxol, carmustine, cisplatin, fluorouracils, polyamine inhibitors, topoisomerase inhibitors, tamoxifene, prodasone, sandostatine, sodium butyrate, mitomycin C, penicillins, β-lactamines, cephalosporines, cyclines, aminoglucosides, macrolides, sulfamides, AZT, protease inhibitors, acyclovir, retrovir and foscarnet.

4. The method according to claim 1, wherein the monocyte derived cells and the chemotherapy drugs are in the form of an injectable solution.

5. The method according to claim 1, further comprising: a) recovering blood derived mononuclear cells directly from blood apheresis or from blood bag collection, followed by centrifugation, to eliminate red blood cell granulocytes and platelets, and to collect peripheral blood leukocytes; b) washing peripheral blood leukocytes obtained at the preceding steps by centrifugation to remove platelets, red blood cells and debris to obtain mononuclear cells; c) resuspending the mononuclear cells obtained in the preceding step in a culture medium, and d) culturing said cells of preceding step for 5 to 10 days to obtain monocyte derived cells and contaminating lymphocytes.

6. The method according to claim 1, wherein said monocyte derived cells have been cultured for 5 to 10 days.

7. A method for the simultaneous, separate, or sequential administration of a preparation for the treatment of cancer or infectious disease in a patient, comprising: administering to said patient an effective amount of said preparation, wherein said preparation comprises the following components: monocyte derived cells, and chemotherapy drugs.

8. The method according to claim 7, wherein said monocyte derived cells and chemotherapy drugs are administered simultaneously.

9. The method according to claim 8, wherein the monocyte derived cells are administered repeatedly up to ten times, with an interval between each administration being between three days to two months.

10. The method according to claim 7, wherein the chemotherapy drug is administered at a dose of 0.1 to 1000 mg/day.

11. The method according to claim 8, wherein said drug is selected from the group consisting of cytotoxic compounds, cytostatic compounds, and compounds inducing apoptosis or cytokines, wherein said drug is administered at a dose of 0.1 to 100 mg/day.

12. The process according to claim 11, wherein the chemotherapy drug is administered repeatedly up to 10 times, with interval between each administration being between one day to two months.

13. The method according to claim 7, wherein the chemotherapy drug and the monocyte derived cells are administered sequentially with said chemotherapy drug being administered before the monocyte derived cells.

14. The method according to claim 13, wherein the interval of time between the administration of the monocyte derived cells and the administration of the chemotherapy drugs is one day to two months.

15. The method according to claim 7, wherein the monocyte derived cells and the chemotherapy drug are administered sequentially with the monocyte derived cells being administered before the chemotherapy drug.

16. The method according to claim 7, wherein the monocyte derived cells are administered before the administration of a vaccine directed to a tumor or infectious antigen.

17. The method according to claim 16, wherein the administration of the monocyte derived cells is preceded by chemotherapy.

18. The method according to claim 15, wherein the interval of time between the administration of the chemotherapy drug and the administration of the monocyte derived cells is one day to two months.

19. The method according to claim 7, further comprising: a) recovering blood derived mononuclear cells directly from blood apheresis or from blood bag collection, followed by centrifugation, to eliminate red blood cell granulocytes and platelets, and to collect peripheral blood leukocytes; b) washing peripheral blood leukocytes obtained at the preceding steps by centrifugation to remove platelets, red blood cells and debris to obtain mononuclear cells; c) resuspending the mononuclear cells obtained in the preceding step in a culture medium, and d) culturing said cells of preceding step for 5 to 10 days to obtain monocyte derived cells and contaminating lymphocytes.

20. The method according to claim 7, wherein said monocyte derived cells have been cultured for 5 to 10 days.

L10 ANSWER 9 OF 21 USPATFULL on STN
2003:240224 Combined preparation for the treatment of neoplasic diseases or of infectious diseases.
Bartholeyns, Jacques, Bures-sur-Yvette, FRANCE
Fouron, Yves, Marlborough, MA, United States
Romet-Lemonne, Jean-Loup, Paris, FRANCE
I.D.M. Immuno-Designed Molecules, Paris, FRANCE (non-U.S. corporation)

US 6616925 B1 20030909
APPLICATION: US 1998-81443 19980519 (9)
PRIORITY: EP 1998-400783 19980402
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A combined preparation consisting essentially of as active substance the following individual components, in the form of a kit-of-parts: cytotoxic macrophages, and at least one chemotherapy drug selected from the group consisting of anthracyclins, daunorubicin, adriamycin, taxoter derivatives, vinca alcaloids, vincristine, taxol, carmustine, cisplatin, fluorouracils, polyamine inhibitors, topoisomerase inhibitors, tamoxifene, prodasone, sandostatine, sodium butyrate, mitomycin C, penicilins, .E-backward.-lactamines, caphalosporines, cyclines, aminoglucosidescosides, macrolides, sulfamides, AZT, protease inhibitors, acyclovir, retrovir and foscarnet; wherein said cytotoxic macrophages are present in said kit-of-parts as a first injectable solution, and wherein said at least one chemotherapy drug is present in said kit-of-parts as a second injectable solution physically separate from said first injectable solution, said macrophages being suspended in said first injectable solution at a concentration yielding a dose of about 107 to about 1010 monocyte derived cells per injection.

2. The combined preparation according to claim 1, wherein the cytotoxic macrophages contain chemotherapy drugs.

3. The combined preparation according to claim 1, wherein the cytotoxic macrophages are prepared according to a method comprising the following steps: 1) recovery of blood derived mononuclear cells directly from blood apheresis or from blood bag collection, followed by centrifugation, to eliminate a substantial part of red blood cells granulocytes and platelets, and collection of peripheral blood leukocytes; 2) washing peripheral blood leukocytes obtained at the preceding steps to obtain mononuclear cells; 3) resuspension of the total mononuclear cells (monocytes+lymphocytes) obtained at the preceding step in culture medium (RPMI or IMDM type) at 106 to 2.107 cells/ml, and culture for 5 to 10 days at 37° C. under O2/CO2 atmosphere in hydrophobic gas permeable bags, to obtain cytotoxic macrophages and contaminating lymphocytes.

4. The combined preparation according to claim 1, wherein the cytotoxic macrophages are administered at a dose of about 108 to about 109.

5. The combined preparation according to claim 1, wherein the cytotoxic macrophages are administered in a repeated way up to ten times, the interval between each administration being between three days to two months.

6. The combined preparation according to claim 1, wherein the chemotherapy drug is administered at a dose of about 0.1 to about 1000 mg/day.

7. The combined preparation according to claim 1, wherein the chemotherapy drug is administered in a repeated way up to 10 times, the interval between each administration being between one day to two months.

8. The combined preparation according to claim 1, wherein the chemotherapy drug and the cytotoxic macrophages are injected simultaneously.

9. The combined preparation according to claim 1, wherein the chemotherapy drug and the cytotoxic macrophages are administered in sequential way, the chemotherapy drug being administered before the cytotoxic macrophages.

10. The combined preparation according to claim 9, wherein the interval of time between the administration of the cytotoxic macrophages and the administration of the chemotherapy drugs is of one day to two months.

11. The combined preparation according to claim 1, wherein the cytotoxic macrophages and the chemotherapy drug are administered sequentially, the cytotoxic macrophages being administered before the chemotherapy drug.

12. The combined preparation according to claim 11, wherein the interval of time between the administration of the chemotherapy drug and the administration of the cytotoxic macrophages is of one day or two months.

13. The combined preparation according to claim 9, wherein the administration of cytotoxic macrophages is followed by an administration of chemotherapy drug.

14. The combined preparation according to claim 13, wherein the interval of time between the administration of cytotoxic macrophages and the administration of chemotherapy drugs is of one day or two months.

L10 ANSWER 10 OF 21 USPATFULL on STN
2003:196943 Monocyte derived cells with immunosuppressive properties, process for their preparation and their uses in pharmaceutical compositions.
Bartholeyns, Jacques, Bures-sur-Yvette, FRANCE
Chokri, Mohamed, Paris, FRANCE
Romet-Lemonne, Jean-Loup, Paris, FRANCE
I.D.M. Immuno-Designed Molecules, Paris, FRANCE (non-U.S. corporation)
US 6596275 B1 20030722
WO 9950394 19991007
APPLICATION: US 2000-647532 20001002 (9)
WO 1999-EP2107 19990329
PRIORITY: EP 1998-400743 19980330
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. Monocyte derived cells which have immunosuppressive properties presenting the following properties: increased the release, with respect to normal monocyte derived cells, of at least one of the compounds selected from the group consisting of PGE-2, IL-10 and IL-4, and decreased the level of expression and secretion of at least one of the inflammatory and immunostimulating cytokines selected from the group consisting of IL-1, IL-12, and IFNγ, with respect to normal monocyte derived cells, and decreased the presence, on their membrane, with respect to normal monocyte derived cells, of at least one of the accessory molecules selected from the group consisting of CD80, CD86, and CD40, and having polylysine-cDNA encoding of myelin protein integrated into the cell nucleus.

2. The monocyte derived cells, with immunosuppressive properties, according to claim 1, wherein the increased release, with respect to normal monocyte derived cells, of at least one of the compounds selected from the group consisting of PGE-2, IL-10 and IL-4 is in an amount higher than 0.1 pg/cells/hr.

3. The monocyte derived cells, which have immunosuppressive properties, according to claim 1, wherein the decreased level, with respect to

immature dendritic cells, macrophages or monocyte derived cells, of expression of and secretion of inflammatory and immunostimulating cytokines selected from the group consisting of IL-1, IL-12 and IFNγ is below 0.01 pg/cell/hr.

4. The monocyte derived cells, which have immunosuppressive properties, according to claim 1, wherein the decreased presence, with respect to normal monocyte derived cells, on the membrane of at least one of the following activation or accessory molecules selected from the group consisting of CD80, CD86, CD40, MHC class I and MHC class II molecule in an amount of less than 10^3 molecules per cell.

5. A pharmaceutical composition comprising, monocyte derived cells which have immunosuppressive properties according to claim 1, in association with a pharmaceutically acceptable vehicle.

6. The pharmaceutical composition according to claim 5, in the form of sterile injectable preparations.

7. The pharmaceutical composition, in the form of an immunotolerant composition comprising, as an active substance, monocyte derived cells which have immunosuppressive properties according to claim 5, having integrated in their nucleus a polylysine-cDNA coding for which tolerance is desired.

8. The monocyte derived cells, which have immunosuppressive properties, according to claim 1, which present the following properties: having polylysine-cDNA encoding for a myelin protein which has been integrated into the nucleus of said monocyte derived cell in the absence of cell division.

L10 ANSWER 11 OF 21 USPATFULL on STN
2003:194124 Method for enhancing the presentation of exogenous antigen by human antigen-presenting cells and opsonized micro particle complexes for applying this method.
Leserman, Lee, Marseille, FRANCE
Nardin, Alessandra, Paris, FINLAND
Abastado, Jean-Pierre, Paris, FRANCE
Bartholeyns, Jacques, Turquant, FRANCE
Machy, Patrick, Marseille, FRANCE
Serre, Karine, Marseille, FRANCE
US 2003133934 A1 20030717
APPLICATION: US 2002-181689 A1 20021104 (10)
WO 2000-EP12993 20001220
PRIORITY: EP 2000-400170 20000121
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. Opsonized micro-particle complex comprising: a micro-particular vector encapsulating at least one antigen and at least one antibody or fragment thereof, with said antibody being a human or humanized antibody or an antibody binding to human FcR with substantially the same affinity and avidity as the ones of a human antibody and with said antibody or fragment thereof having the carboxy terminal end of its Fc portion external with respect to the opsonized micro particle complex.

2. Opsonized micro particle complex according to claim 1, wherein the antibody is bound to the micro-particular vector through its variable portion.

3. Opsonized micro particle complex according to claim 1 or 2, wherein

the micro-particular vector encapsulating the antigen bears determinants and the antibody is bound to the micro-particular vector through its variable portion specific of said determinants.

4. Opsonized micro particle complex according to claim 1, wherein the antibody is directly linked to the micro-particular vector by its Fc portion, with the carboxy terminal end of the Fc portion being external with respect to the opsonized micro particle complex.

5. Opsonized micro particle complex according to any one of claims 1 to 4, wherein the micro-particular vector is a liposome or a micro particle, advantageously having a size of about 20 to about 1000 nm.

6. Opsonized micro particle complex according to anyone of claims 1 to 5, wherein the micro-particular vector contains at least one destabilizing agent for the membrane of the endocytic vesicle, for the improvement of the delivery of the antigen contained in said micro-particular vector, with said destabilizing agent being, for instance, proteins, peptides or lipids of viral or synthetic origin.

7. Opsonized micro particle complex according to any one of the claims 1 to 6, wherein the determinant is a peptide, a polypeptide, a sugar molecule, DNP or another determinant.

8. Opsonized micro particle complex according to any one of claims 1 to 7, wherein the antibody is a human or humanized antibody.

9. Opsonized micro particle complex according to any one of the claims 1 to 8, wherein the antigen is a tumor antigen or an antigen relevant in auto immune or infectious diseases or an allogenic antigen and preferably a combination of tumor antigens.

10. Opsonized micro particle complex according to any one of the claims 1 to 9, wherein the antigen-presenting cell is a dendritic cell, and particularly monocyte-derived immature dendritic cells.

11. Combined preparation containing as active substance the following individual components, in the form of a kit of parts: a micro-particular vector encapsulating at least one antigen at least one antibody or fragment thereof, with said antibody being a human or humanized antibody or an antibody binding to human FcR with substantially the same affinity and avidity as the ones of a human antibody, and being liable to bind to said micro-particular vector, in such a way that the antibody or fragment thereof has the carboxy terminal end of its Fc portion which remains free, possibly human antigen presenting cells bearing Fc receptors, liable to bind to the above-mentioned free Fc portion of the antibody or fragment thereof, for the simultaneous, separate or sequential use, in the vaccination against cancer, infectious or autoimmune diseases.

12. Ternary complex between the opsonized micro particle complex according to any one of claims 1 to 10, and a human antigen presenting cell bearing Fc receptors, wherein the opsonized micro particle complex is bound to the antigen presenting cell Fc receptor through the carboxy terminal end of Fc portion of the antibody.

13. Use of an opsonized micro particle complex, according to any one of claims 1 to 10, or of a ternary complex according to claim 12 as a drug, particularly as a vaccine.

14. Vaccine comprising as active substance an opsonized micro particle complex according to any one of claims 1 to 10, or a ternary complex

according to claim 12, possibly in association with a pharmaceutically acceptable vehicle.

15. Use of an opsonized micro particle complex according to any one of claims 1 to 10, or of a ternary complex according to claim 12, for the preparation of a vaccine against cancer, infectious or auto-immune disease.

16. Method for in vitro, or ex vivo targeting antigens to human antigen presenting cells allowing antigen presentation via MHC class I pathway, comprising the step of contacting an opsonized micro particle complex according to any one of claims 1 to 10, with human antigen presenting cells, to form a ternary complex between the opsonized micro particle complex and said human antigen presenting cells.

17. Method for in vitro, or ex vivo targeting antigens to human antigen presenting cells allowing antigen presentation via MHC class I pathway, comprising the step of contacting a micro-particular vector encapsulating at least one antigen, at least one antibody or fragment thereof, with said antibody being a human or humanized antibody or an antibody binding to human FcR with substantially the same affinity and avidity as the ones of a human antibody and liable to bind to the micro-particular vector in such a way that the carboxy terminal end of its Fc portion is external with respect to the opsonized micro-particle complex, and human antigen presenting cells, to form a ternary complex between the micro-particular vector, the antibody and the human antigen presenting cells.

18. Method according to any one of the claims 16 or 17, wherein the antigen presentation via MHC class II is also involved.

19. Method according to any one of the claims 16 to 18, wherein the stimulation of human CD8+ T cells specific for exogenous antigen is involved.

L10 ANSWER 12 OF 21 USPATFULL on STN
2003:158921 Macrophages, process for preparing the same and their use as active substances of pharmaceutical compositions.
Chokri, Mohamed, Deuil-La-Barre, FRANCE
Bartholeyns, Jacques, Bures-Sur-Yvette, FRANCE
I.D.M. Immuno-Designed Molecules, Paris, FRANCE (non-U.S. corporation)
US 2003108534 A1 20030612
APPLICATION: US 2003-336726 A1 20030106 (10)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A method of treating cancer, comprising administering to a patient in need of said treatment, an effective amount of macrophages produced by culturing monocytes in vitro, said macrophages having at least one of the following properties: their cytotoxic activity without IFN-γ is increased by about 20 to 30% with respect to standard macrophages; their cytotoxic activity is increased with IFN-γ by about 20 to 40% with respect to standard macrophages; deactivation of the cytotoxic activity following activation of IFN-γ is such that sixty hours after activation with IFN-γ, the residual cytotoxic activity is at least 30% of the maximum cytotoxic activity presented by the macrophages due to IFN-γ activation, with said cytotoxic activity being measured as a percentage of the inhibition of 3-H thymidine incorporation by target tumoral cells, particularly U 937 cells.

2. The method as claimed in claim 1, wherein said effective amount is

about 108 to about 5x109 macrophages.

3. The method as claimed in claim 1, wherein said effective amount is about 2x109 to about 5x109 macrophages.

4. The method as claimed in claim 1, wherein the said method further comprises administering lymphocytes to said patient.

5. The method according to claim 1, wherein said macrophages contain exogenous nucleic acids and/or drugs.

L10 ANSWER 13 OF 21 USPATFULL on STN
2003:89117 Macrophages, process for preparing the same and their use as active substances of pharmaceutical compositions.
Chokri, Mohamed, Deuil-la-Barre, FRANCE
Bartholeyns, Jacques, Bures-sur-Yvette, FRANCE
I.D.M. Immuno-Designed Molecules, Paris, FRANCE (non-U.S. corporation)
US 6540994 B1 20030401
APPLICATION: US 1999-304563 19990504 (9)
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A method of treating cancer, comprising administering to a patient in need of said treatment, an effective amount of macrophages produced by culturing monocytes in vitro, said macrophages having at least one of the following properties: their cytotoxic activity without IFN-γ is increased by about 20 to 30% with respect to standard macrophages; deactivation of the cytotoxic activity following activation of IFN-γ is such that sixty hours after activation with IFN-γ, the residual cytotoxic activity is at least 30% of the maximum cytotoxic activity presented by the macrophages due to IFN-γ activation, with said cytotoxic activity being measured as a percentage of the inhibition of 3-H thymidine incorporation by target tumoral cells, wherein said effective amount is about 2x109 to about 5x109 macrophages, the method further comprising administering lymphocytes to said patient in an amount of about 4x109 to about 10x109 lymphocytes.

2. A method as claimed in claim 1, wherein said macrophages contain exogenous nucleic acids and/or drugs.

3. A method as claimed in claim 1, wherein the target tumoral cells are U937 cells.

L10 ANSWER 14 OF 21 USPATFULL on STN
2002:336839 Antigen presenting cells, a process for preparing the same and their use as cellular vaccines.
Chokri, Mohamed, Strasbourg, FRANCE
Bartholeyns, Jacques, Bures-Sur-Yvette, FRANCE
Romet-Lemonne, Jean-Loup, Paris, FRANCE
I.D.M. IMMUNO-DESIGNED, Paris, FRANCE (non-U.S. corporation)
US 2002192193 A1 20021219
APPLICATION: US 2002-195066 A1 20020715 (10)
PRIORITY: EP 1998-96401099 19980521
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A method of clinically treating a patient, comprising: administering to said patient an effective amount of monocyte derived antigen presenting cells (MD-APCs) which present the following properties: the

presence on the MD-APC cell surface of surface antigens CD80 and CD86, and the presence on the MD-APC cell surface of surface antigens CD40 and mannose receptor.

2. The method according to claim 1, wherein said MD-APCs present the following properties: a higher phagocytic capacity than mature dendritic cells, and a greater capability of stimulating proliferation of allogenic lymphocytes relative to standard macrophages.

3. The method according to claim 2, wherein said mononuclear cells present IL 13 receptors on their surface.

4. The method according to claim 1, wherein said MD-APCs are administered in an amount of about 108 to about 5x109 MD-APCs.

5. The method according to claim 1, further comprising administering lymphocytes to said patient.

6. The method according to claim 5, wherein said lymphocytes are administered to said patient in an amount of about 4x109 to about 10x109 lymphocytes.

7. The method according to claim 5, wherein said lymphocytes are administered simultaneously, separate 14 or sequential 14 to said MD-APCs.

8. A method of clinically treating a patient, comprising: administering to said patient an effective amount monocyte derived cells (MD-APCs) which present the following properties: a higher phagocytic capacity than mature dendritic cells, and a greater capability of stimulating proliferation of allogenic lymphocytes relative to standard macrophages.

9. The method according to claim 8, wherein said MD-APCs present surface antigens CD80 and CD 86 on their surface.

10. The method according to claim 8, wherein said MD-APCs present surface antigens CD40 and mannose receptor on their surface.

11. The method according to claim 8, wherein said mononuclear cells present IL 13 receptors on their surface.

12. The method according to claim 8, wherein said MD-APCs are administered in an amount of about 108 to about 5x109 MD-APCs.

13. The method according to claim 8, further comprising administering lymphocytes to said patient in an amount of about 4x109 to about 10x109 lymphocytes.

14. The method according to claim 13, wherein said lymphocytes are administered simultaneously, separate 14 or sequential 14 to said MD-APCs.

15. A method of clinically treating a patient, comprising: administering to said patient an effective amount monocyte derived cells (MD-APCs) which present the following properties: the presence on the MD-APC cell surface of surface antigens CD80 and CD 86, the presence on the MD-APC cell surface of surface antigens CD40 and mannose receptor, and the presence on the MD-APC cell surface of surface antigen CD 14.

16. The method according to claim 15, wherein said MD-APCs present the

following properties: a higher phagocytic capacity than mature dendritic cells, and a greater capability of stimulating proliferation of allogenic lymphocytes relative to standard macrophages.

17. The method according to claim 18, wherein said mononuclear cells present IL 13 receptors on their surface.

18. The method according to claim 16, wherein said MD-APCs are administered in an amount of about 10⁸ to about 5×10⁹ MD-APCs.

19. The method according to claim 16, further comprising administering lymphocytes to said patient in an amount of about 4×10⁹ to about 10×10⁹ lymphocytes.

20. The method according to claim 19, wherein said lymphocytes are administered simultaneously, separate or sequential to said MD-APCs.

21. A method according to claim 1, wherein said MD-APCs have been loaded with a material coding for a relevant antigen or with a relevant antigen.

L10 ANSWER 15 OF 21 USPATFULL on STN
2002:336838 Antigen presenting cells, a process for preparing the same and their use as cellular vaccines.
Chokri, Mohamed, Strasbourg, FRANCE
Bartholeyns, Jacques, Bures-Sur-Yvette, FRANCE
Romet-Lemonne, Jean-Loup, Paris, FRANCE
I.D.M. IMMUNO-DESIGNED, PARIS, FRANCE (non-U.S. corporation)
US 2002192192 A1 20021219
APPLICATION: US 2002-195065 A1 20020715 (10)
PRIORITY: EP 1998-96401099 19980521
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A method of preparing monocyte derived antigen presenting cells (MD-APCs), comprising: preparing a culture of mononuclear cells in a culture medium comprising a chemical ligand of mononuclear cells, allowing said mononuclear cells to differentiate into MD-APCs which present the following properties: the presence on the MD-APC cell surface of surface antigens CD80 and CD86, and the presence on the MD-APC cell surface of surface antigens CD40 and mannose receptor.

2. The method according to claim 1, wherein the culture medium comprises IL-13, or ligands to IL-13 receptors.

3. The method according to claim 1, wherein the culture medium further comprises GM-CSF and IL-13 or ligands to IL-13 receptors.

4. The method according to claim 2, wherein the culture medium further comprises GM-CSF and IL-13 or ligands to IL-13 receptors.

5. The method according to claim 1, wherein said mononuclear cells present IL 13 receptors on their surface.

6. The method according to claim 1, wherein the culture medium contains chemical ligands of mononuclear cells selected from the group consisting of histamine, cimetidine and a H_2 antagonist without GM-CSF.

7. The method according to claim 1, wherein the culture medium contains chemical ligands of mononuclear cells selected from the group consisting

of histamine, cimetidine and a H2 antagonist, each in combination with GM-CSF.

8. The method of claim 7, wherein the culture medium contains 50 to 1000 UI/ml, preferably 500 UI/ml of GM-CSF.

9. The method according to claim 1, further comprising: isolating leukocytes from peripheral blood apheresis and reducing platelet contamination and anticoagulants from the apheresis product, and isolating mononuclear cell monocytes and lymphocytes from red cells and granulocytes in order to have less than 10% granulocytes and less than 5% red cells before culturing said mononuclear cells.

10. The method according to claim 1, wherein said mononuclear cells are maintained in said culture medium for 5 to 15 days.

11. The method according to claim 1, wherein said MD-APCs present the following properties: a higher phagocytic capacity than mature dendritic cells, and a greater capability of stimulating proliferation of allogenic lymphocytes relative to standard macrophages.

12. A method of preparing monocyte derived cells (MD-APCs), comprising: preparing a culture of mononuculear cells in a culture medium comprising a chemical ligand of mononuclear cells, allowing said mononuclear cells to differentiate into MD-APCs which present the following properties: a higher phagocytic capacity than mature dendritic cells, and a greater capability of stimulating proliferation of allogenic lymphocytes relative to standard macrophages,

13. The method according to claim 12, wherein said MD-APCs present surface antigens CD80 and CD 86 on their surface.

14. The method according to claim 12, wherein said MD-APCs present surface antigens CD40 and mannose receptor on their surface.

15. The method according to claim 12, wherein the culture medium further comprises GM-CSF and IL 13 or ligands to IL13 receptors.

16. The method according to claim 15, wherein said mononuclear cells present IL 13 receptors on their surface.

17. A method of preparing a composition comprising monocyte derived cells (MD-APCs), comprising: preparing a culture of mononuclear cells in a culture medium comprising a chemical ligand of mononuclear cells, allowing said mononuclear cells to differentiate into MD-APCs which present the following properties: the presence on the MD-APC cell surface of surface antigens CD80 and CD 86, the presence on the MD-APC cell surface of surface antigens CD40 and mannose receptor, and the presence on the MD-APC cell surface of surface antigen CD 14.

18. The method according to claim 17, wherein said MD-APCs present the following properties: a higher phagocytic capacity than mature dendritic cells, and a greater capability of stimulating proliferation of allogenic lymphocytes relative to standard macrophages.

19. The method according to claim 17, wherein the culture medium comprises GM-CSF and IL-13 or ligands of IL-13 receptors.

20. The method according to claim 19, wherein said mononuclear cells present IL-13 receptors on their surface.

21. The method according to claim 17, wherein said mononuclear cells are

maintained in said culture medium for 5 to 15 days.

22. A method according to claim 1, wherein the culture medium of MD-APCs is added with crude antigens, peptides, CDNA, genetic material or bispecific antibodies.

L10 ANSWER 16 OF 21 USPATFULL on STN
2002:322561 NEW ANTIGEN PRESENTING CELLS, A PROCESS FOR PREPARING THE SAME AND THEIR USE AS CELLULAR VACCINES.
CHOKRI, MOHAMED, STRASBOURG, FRANCE
BARTHOLEYNS, JACQUES, BURES-SUR-YVETTE, FRANCE
ROMET-LEMONNE, JEAN-LOUP, PARIS, FRANCE
US 2002182725 A1 20021205
APPLICATION: US 1998-194053 A1 19981123 (9)
WO 1997-EP2703 19970515
PRIORITY: EP 1998-96401099 19980521
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. MD-APCs which have the following properties they present on their surface: antigen CD14 and CD64 with a mean intensity of about 5 to about 200, antigen CD80 and CD86 with a mean intensity of about 20 to about 200, antigen cd40 and mannose receptor with a mean intensity of 50 to 500, they are substantially devoid of the surface antigens CD1a and CD1c, the presence and mean intensities respectively of CD14, CD64, CD80, cd86 being for instance determined by immunofluorescence staining and flow cytometry analysis, they present a phagocytosis property such as determined by the following test: said phagocytosis capacity being evaluated by an uptake of formalin fixed yeast, for example by culturing macrophages for 2 hours, adding yeast in 1/10 macrophages/yeast ratio and incubating at 37° C., 5% C02 atmosphere for 2-3 hours fixing by the May-Grunwald-Giemsa (MGG) staining, and the percentage of phagocytic MD-APCs being quantified for instance by microscopic analysis, they have the property of stimulating the proliferation of allogenic lymphocytes such as determined by the following test allogenic primary mixed lymphocytes reaction (MLR) was carried out in 96-well microtiter plates by adding different numbers (2x103 to 2xlO5 in 100 il medium/well) of MD-APCs to 2x105 in 100 pl medium/well of allogenic T cells purified from buffy coats and after 5 days incubation at 37° C., cell proliferation was assessed by a colorimetric method, such as the hydrolysis of tetrazolium salt WST-1 (Boehringer Mannheim, Germany), (slightly red) to Formozan (dark red).

2. MD-APCs according to claim 1, which present, on their surface, antigen MHC-II with a mean intensity of about 100 to about 400, such as determined by immunofluorescence staining and flow cytometry analysis.

3. MD-APCs according to any one of claims 1 or 2, which are substantially devoid of surface antigen CD83, such as determined by immunofluorescence staining and flow cytometry analysis.

4. MD-APCs according to any one of claims 1 to 3, which present adherent properties such as determined by the following test: the macrophages are cultured for 2 h in culture medium (I.M.D.M. or R.P.M.I.) on plastic flasks and the percentage (%) of adherent cells is quantified for instance by microscopic analysis.

5. MD-APCs culture wherein: about 10% to about 50% of the MD-APCs present antigen CD14 on their surface, about 10% to about 50% of the MD-APCs present antigen CD64 on their surface, about 30% to about 100% of the MD-APCs present antigens CD80 and CD86 on their surface, about

80% to about 100% of the MD-APCs present antigen MHC-II on their surface, about 70% to about 100% of the MD-APCs present adherent properties, about 30% to about 100% of the MD-APCs present a phagocytosis property, each MD-APCs having the above-mentioned properties being such that said properties are expressed according to the intensities as specified in any one of claims 1 to 4.

6. Process for preparing a composition comprising MD-APCs according to any one of claims 1 to 5, comprising the culture of mononuclear cells in a culture medium containing chemical ligands of mononuclear cells, such as histamine or-histamine agonist and a H2 antagonist, in combination or not with "additional" GM-CSF, or other chemical ligands interacting with mononuclear cells and allowing differentiation into MD-APCs, such as detoxified LPS such as lipid A, C3 and other ligands of complement receptors, taxols, oxydoreductors such as flavenoids or polyphenols, ligands to CD40, to the TNF receptors or to vitamin D3 receptors.

7. Process according to claim 6, wherein the culture medium contains chemical ligands of mononuclear cells, for example histamine and cimetidine or a H2 antagonist without "additional" GM-CSF, histamine being present at a concentration of about 1031 2 M to about 10-6 M, preferably of about 10-4 M, and cimetidine or the H2 antagonist being present at a concentration of about 10-4 M to about 10-9 M, preferably of about 10-6 M.

8. Process according to claim 6, wherein the culture medium contains chemicals ligands of mononuclear cells, for example histamine and cimetidine or a H2 antagonist, in combination with "additional" GM-CSF, histamine being present at a concentration of about 1031 2 M to about 10-6 M, preferably of about 10-4 M, cimetidine or the H2 antagonist being present at a concentration of about 10-4 M to about 10-9 M, preferably of about 10-6 M, and additional GM-CSF being present at a concentration of about 50 U/ml to about 2000 U/ml, preferably of about 500 U/ml.

9. Process according to any one of claims 6 to 8, comprising isolation of leukocytes, from healthy donors or from patients, from peripheral blood by apheresis and removal platelets and anticoagulant from the apheresis product, isolation of mononuclear cells (monocytes+lymphocytes) from red cells and granulocytes in order to have less than 10% granulocytes and less than 5% red cells, culture of the mononuclear cells obtained at the previous stage by placing them in an appropriate culture medium containing chemical ligands of mononuclear cells, such as histamine or an agonist of histamine, an H2 antagonist, such as cimetidine, in combination or not with GM-CSF, for a time sufficient to obtain differentiated MD-APCs, preferably for about 5 to 15 days, and possibly separating the MD-APCs from the lymphocytes, and recovering the MD-APCs or the macrophages and lymphocytes.

10. Process according to any one of claims 6 to 9, wherein the culture medium of MD-APCs is added with crude antigens, for instance autologous tumor membrane, killed tumoral cells, bacterial capsides, viral homogenates cleared from nucleic acids, specific peptides against which an immune response is desired, cDNA or genetic material linked to vectors (for example gluconated polylysine) to allow transfection of the MD-APCs with material coding for the relevant peptide or protein to be presented on the macrophage membrane and against which an immune response is desired, or bispecific antibodies targeting on the one side, a surface antigen of the MD-APCs and, on the other side, a relevant antigen against which an immune response is desired.

11. MD-APCs liable to be obtained according to the process of any one of claims 6 to 10.

12. Pharmaceutical compositions containing as active substance, MD-APCs according to any one of claims 1 to 5 or 11.

13. Cellular vaccine compositions containing as active substance, MD-APCs according to any one of claims 1 to 5 or 11.

14. Medium containing elements necessary for the growth and differentiation of monocytes into MD-APCs according to claims 1 to 5 or 11, and in addition containing chemical ligands of mononuclear cells, for example histamine, cimetidine in combination or not with GM-CSF.

15. Cell processor or kit containing means for the recovery of lymphocytes and monocytes free of contaminants, appropriate buffer and wash solutions and possibly appropriate means for the conservation of MD-APCs, means for preparing a culture for the monocytes and possibly the lymphocytes and containing chemical ligands of mononuclear cells, for example histamine, cimetidine or a H2 antagonist in combination or not with GM-CSF, possibly means for transfection of cultured cells and means for targeting antigens to MD-APCs.

16. Cell processor or kit according to claim 15, containing means for recovering and centrifuging blood to obtain a leukocyte concentrate, means for separating lymphocytes and monocytes from the other white cells and for eliminating the contaminating red cells, culture medium for MD-APCs and possibly lymphocytes with complements and particularly chemical ligands of mononuclear cells, for example histamine and cimetidine or a H2 antagonist, in combination or not with GM-CSF, appropriate means for the conservation of MD-APCs, appropriate buffer and wash solution.

17. Products containing MD-APCs according to any one of claims 1 to 5 or 11, and lymphocytes, as a combined preparation for simultaneous, separate or sequential use in cell therapy.

18. Products according to claim 17, characterized in that they contain the MD-APCs and the lymphocytes in a ratio of at least 20% to 50% of MD-APCs expressed in cell number.

19. Method for the clinical treatment, comprising the administration of an appropriate amount of MD-APCs according to any one of claims 1 to 5 or 11. and preferably in an amount of about 108 to about 5x109 MD-APCs.

20. Method according to claim 19 for the treatment of any disorder comprising the administration of lymphocytes in an amount of about 4x109 to about 10x109 lymphocytes.

21. Use of chemical ligands of mononuclear cells, for example an agonist of histamine, in particular histamine, and a H2 antagonist, in particular cimetidine, in combination or not with GM-CSF, for the preparation of MD-APCs having the following properties they present on their surface antigen CD14 and CD64 with a mean intensity of about 5 to about 200, antigen CD80 and CD86 with a mean intensity of about 20 to about 200, antigen CD40 and mannose receptor with a mean intensity of 50 to 500. they are substantially devoid of the surface antigens CD1a and CD1c, the presence and mean intensities respectively of CD14, CD64, CD80, CD86 and the absence of CD1a and CD1c being for instance determined by imrnunofluorescence staining and flow cytometry analysis, they present high phagocytosis property such as determined by the

following test : said phagocytosis capacity being evaluated by an uptake of formalin fixed yeast, for example by culturing MD-APCs for 2 hours to select adherent cells, adding yeast in {fraction (1/10)} mMD-APCs/yeast ratio and incubating at 37° C., 5% CO2 atmosphere for 2-3 hours fixing by the May-Grunwald-Giemsa (MGG) staining, and the percentage of phagocytic MD-APCs being quantified for instance by microscopic analysis, they have the property of stimulating the proliferation of allogenic lymphocytes such as determined by the following test allogenic primary mixed lymphocytes reaction (MLR) was carried out in 96-well microtiter plates by adding different numbers (2x103 to 2x105 in 100 tul medium/well) of MD-APCs to 2x105 in 100 HI medium/well of allogenic T cells purified from buffy coats and after 5 days incubation at 37° C., cell proliferation was assessed by a colorimetric method, such as the cleavage of tetrazolium salt WST-1 (slightly red) to Formozan (dark red) or such as Brdu incorporation during DNA synthesis.

L10 ANSWER 17 OF 21 USPATFULL on STN
2002:300804 USE OF MONOCYTES DERIVED CELLS, ANTIGENS AND ANTIBODIES FOR OPTIMAL INDUCTION OF IMMUNOTHERAPEUTIC EFFICIENCY.
BARTHOLEYNS, JACQUES, BURES-SUR-YVETTE, FRANCE
FOURON, YVES, MARLBOROUGH, MA, UNITED STATES
US 2002168347 A1 20021114
APPLICATION: US 1998-80698 A1 19980518 (9)
PRIORITY: EP 1998-4008839 19980409
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. Monocyte derived cells, in a purified form and substantially free of contaminants, presenting antigenic epitopes on their membranes after interiorization and processing of at least an antigen-antibody complex formed between an antigen and an antibody, under appropriate conditions, said epitopes corresponding to proteolytic degradation products of said antigen, with said antibody being directed against a tumor or against an infectious agent, and with said antigen being fragments of tumor or of infectious agent, including membranes or tumor apoptotic bodies, or purified tumor or infectious antigens or being recombinant tumor or infectious antigens.

2. Process for the preparation of monocyte derived cells presenting antigenic epitopes on their membranes after interiorization and processing of at least an antigen-antibody complex, formed between an antigen and an antibody, said process comprising the following steps: a) preparation of the monocytes derived cells according to the following method: 1) recovery of blood derived mononuclear cells directly from blood apheresis or from blood bag collection, followed if necessary by centrifugation, to eliminate a substantial part of red blood cells granulocytes and platelets, and collection of peripheral blood leukocytes; 2) washing peripheral blood leukocytes obtained at the preceeding steps for instance by centrifugation (to remove 90% of platelets, red blood cells and debris) to obtain mononuclear cells; 3) resuspension of the total mononuclear cells obtained at the preceeding step in culture medium (RPMI or IMDM type) at 106 to 2.107 cells/ml, possibly completed by cytokines and/or autologous serum, and culture for 5 to 10 days at 37° C. under O2/CO2 atmosphere in hydrophobic gas permeable bags, to obtain monocyte derived cells and contaminating lymphocytes; b) addition of antigens and antibodies to the monocyte derived cells obtained at the preceeding step to form a ternary complex between monocyte derived cells, an antigen and an antibody; c) incubation of said ternary complex for a time and at a temperature sufficient to allow endocytosis into intracellular vacuoles

of the monocyte derived cells and processing of the antigen-antibody complex, with said processing consisting of digestion of the antigen-antibody complex and association of the epitopes of the antigen resulting from the digestion with MHC molecules, to obtain monocyte derived cells presenting antigenic epitopes on their membranes.

3. Process according to claim 2, wherein said antibody is directed against a tumor or against an infectious agent, with said antigen is fragments of tumor or of infectious agent, including membranes or tumor apoptotic bodies, or purified tumor or infectious antigens or is a recombinant tumor or infectious antigen.

4. Process according to claim 2, wherein in the step of addition, said antigens and antibodies are in the form of a complex.

5. Process according to anyone of claims 1 to 4, comprising the additional following step: d) centrifugation of the monocyte derived cells presenting antigenic epitopes on their membranes, washing and resuspension, for instance in isotonic medium, to obtain a suspension of the above defined monocyte derived cells.

6. Process according to claim 5, wherein the step of centrifugation is followed by e) freezing at temperature below or equal to -80° C. aliquots of the above said suspension, with the addition of a cryopreservative.

7. Process according to claim 6, wherein the step of freezing is followed by f) melting said above frozen aliquots at a temperature enabling to obtain a suspension of monocyte derived cells presenting antigenic epitopes on their membranes, for instance at 4° C., washing said suspension and resuspending it, for instance in an isotonic medium, to obtain a suspension of monocyte derived cells presenting antigenic epitopes on their membranes.

8. Process according to anyone of claims 2 to 7, wherein the antibodies are human or humanised IgG, IgA or preferably IgM (for induction of primary immune response) directed against tumor antigens or against infectious antigens (viral or bacterial).

9. Process according to anyone of claims 2 to 7, wherein the antigens are purified tumor, viral or bacterial antigens (polypeptides, glycopeptides, oligosacharides) or membrane fragments serving as complex antigens.

10. Process according to claims 8 or 9, wherein the antigens are pan tumor antigens present on different tumor types.

11. Ternary complex in a purified form, and substantially free of contaminants, between monocytes derived cells, an antigen and an antibody with said antibody being directed against a tumor or against an infectious agent, with said antigen being fragments of tumor or of infectious agent including membranes or tumor apoptotic bodies, or purified tumor or infectious antigens or being recombinant tumor or infectious antigens, and with said antigen and said antibody being liable to form an antigen-antibody complex under appropriate conditions.

12. Process for the preparation of a ternary complex between monocyte derived cells, an antigen and an antibody according to claim 11, comprising the following steps: 1) recovery of blood derived mononuclear cells directly from blood apheresis or from blood bag collection, followed if necessary by centrifugation, to eliminate a substantial part of red blood cells granulocytes and platelets, and

collection of peripheral blood leukocytes; 2) washing peripheral blood leukocytes obtained at the preceeding steps for instance by centrifugation (to remove 90% of platelets, red blood cells and debris) to obtain mononuclear cells; 3) resuspension of the total mononuclear cells obtained at the preceeding step in culture medium (RPMI or IMDM type) at 106 to 2.107 cells/ml, possibly completed by cytokines and/or autologous serum, and culture for 5 to 10 days at 37° C. under O2/CO2 atmosphere in hydrophobic gas permeable bags, to obtain monocyte derived cells and contaminating lymphocytes; b) addition of antigens and antibodies to the monocyte derived cells obtained at the preceeding step to form of a ternary complex between monocyte derived cells, an antigen and an antibody.

13. Process according to claim 12, wherein said antigens and antibodies being either in the form of a complex or not.

14. Monocyte derived cells presenting antigenic epitopes on their membranes such as obtained according to the process of anyone of claims 2 to 10.

15. Ternary complex between monocyte derived cells, an antigen and an antibody such as obtained according to claims 13 or 14.

16. Pharmaceutical composition containing as active substance monocyte derived cells presenting antigenic epitopes on their membranes according to claims 1 or 14, in association with a pharmaceutically acceptable vehicle.

17. Pharmaceutical composition containing as active substance a ternary complex according to claim 15, in association with a pharmaceutically acceptable vehicle.

18. Pharmaceutical composition according to claims 16 or 17, in the form of sterile injectable preparations.

19. Vaccine containing as active substance monocyte derived cells presenting antigenic epitopes on their membranes according to claims 1 or 14, or a ternary complex according to claim 15, in association with a pharmaceutically acceptable vehicle.

20. Use of monocyte derived cells according to claims 1 or 14, or of a ternary complex according to claim 15, for the preparation of a medicament for treating cancer or infectious diseases.

21. Method for the treatment or prevention of cancer comprising the use of monocyte derived cells according to claims 1 or 14, or of a ternary complex according to claim 15.

22. Method for the treatment or prevention of viral or bacterial infections comprising the use of monocyte derived cells according to claims 1 or 14, or of a ternary complex according to claim 15.

23. Method according to claims 21 or 22, wherein the monocyte derived cells or ternary complex are administered systemically, subcutaneously, intravenously or in mucosal or lymphoid tissues.

24. Method for inducing or increasing an immune response comprising the use of monocyte derived cells according to claims 1 or 14, or the use of ternary complex according to claim 15.

L10 ANSWER 18 OF 21 USPATFULL on STN

2002:129783 Monocyte derived cells with immunostimulating properties, their preparation and uses.
Bartholeyns, Jacques, Bures-sur-Yvette, FRANCE
Chokri, Mohamed, Paris, FRANCE
Latour, Nathalie, Braine I'Alleud, BELGIUM
I.D.M. Immuno-Designed, Paris, FRANCE (non-U.S. corporation)
US 6399372 B1 20020604
WO 9950391 19991007
APPLICATION: US 2000-647534 20001002 (9)
WO 1999-EP2106 19990329 20001002 PCT 371 date
PRIORITY: EP 1998-400742 19980330
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. Isolated monocyte derived cells having immunostimulating properties and presenting the following properties: increased release, with respect to unstimulated monocyte derived cells which have not been exposed to chemical or physical stress, of IL12, and increased presence, on their membranes, with respect to unstimulated monocyte derived cells, of the following molecules: MHC class I and MHC class II molecules, accessory molecule CD40 and at least one of the following activation markers CD80, CD83, and CD86.

2. Isolated monocyte derived cells having immunostimulating properties according to claim 1, loaded with exogenous compounds selected from the group consisting of drugs, proteins, growth factors and DNA coding for a protein.

3. Isolated monocyte derived cells having immunostimulating properties according to claim 1, wherein the activation markers are present in an amount of at least 1000 molecules/cells.

4. Isolated monocyte derived cells having immunostimulating properties according to claim 1, wherein the polypeptides, proteins or compounds are released in an amount higher than 1 pg/cell/hr and the activation markers are present in the range of 103 to 105 molecules/cell.

5. Process for conferring immunostimulating properties to macrophages, comprising the step of stimulating said macrophages by physical means selected from the group consisting of thermal stress (heating at 40° C. to 50° C. for at least 30 minutes), pressure change (from 1 bar to 10 bars), microwaves, electric shock (1 to 10 seconds at 250 mV), and electropulsation.

6. Process for the preparation of isolated monocyte derived cells having immunostimulating properties, comprising the steps: 1) recovering blood derived mononuclear cells directly from blood apheresis or from blood bag collection, followed by optional centrifugation, to eliminate a substantial part of red blood cells, granulocytes and platelets, and collection of peripheral blood leukocytes; 2) washing peripheral blood leukocytes obtained at the preceding steps to obtain mononuclear cells; 3) resuspending the cells (monocytes+lymphocytes) obtained at the preceding step in culture medium (AIM-V, RPMI or IMDM type) at 106 to 2x107 cells/ml, completed by cytokines and/or autologous serum, and culture for 5 to 10 days at 37° C. under O2/CO2 atmosphere in hydrophobic gas permeable bags, to obtain monocyte derived cells and contaminating lymphocytes; stimulating said monocyte derived cells by physical means selected from the group consisting of thermal stress (heating at 40° C. to 50° C. for at least 30 minutes), pressure change (from 1 bar to 10 bars), microwaves, electric shock (1 to 10s at 250 mV), or electropulsation for a time sufficient to induce the stimulation of the cell or integration

of exogenous nucleic acid into the DNA of the monocyte derived cell.

7. Process for the preparation of isolated monocyte derived cells with immunostimulating properties, comprising the steps: 1) recovering blood derived mononuclear cells directly from blood apheresis or from blood bag collection, followed by optional centrifugation, to eliminate a substantial part of red blood cells, granulocytes and platelets, and collection of peripheral blood leukocytes; 2) washing peripheral blood leukocytes obtained at the preceding steps to obtain mononuclear cells; 3) resuspending the cells (monocytes+lymphocytes) obtained at the preceding step in culture medium (RPMI or IMDM type) at 106 to 2x107 cells/ml, possibly completed by cytokines and/or autologous serum, and culture for 5 to 10 days at 37° C. under O2/CO2 atmosphere in hydrophobic gas permeable bags, to obtain monocyte derived cells and contaminating lymphocytes; stimulating said monocyte derived cells by addition of chemicals, which induce IFN production said chemicals being selected from the group consisting of double stranded RNA, bacterial or mycobacterial extracts and bacterial type DNA.

8. Process for the preparation of isolated monocyte derived cells with immunostimulating properties according to claim 6, comprising, before the step of stimulating, the step of culturing of said monocyte derived cells and contaminating lymphocytes for 2 to 24 hours, in the presence of drugs, proteins or antigens to interiorize these compounds in said monocyte derived cells.

9. Process for the preparation of isolated monocyte derived cells with immunostimulating properties according to claim 6, comprising the additional step of centrifuging the isolated monocyte derived cells with immunostimulating properties at a temperature of 4° C., said temperature enabling cell preservation, and resuspension in isotonic medium containing autologous serum.

10. Process for the preparation of isolated monocyte derived cells with immunostimulating properties according to claim 6, comprising the additional steps of: centrifuging the isolated monocyte derived cells with immunostimulating properties at a temperature of 4° C., said temperature enabling cell preservation, and resuspending the isolated monocyte derived cells with immunostimulating properties in isotonic medium containing autologous serum, and freezing at a temperature of at least -80° C. aliquots of the isolated monocyte derived cells with immunostimulating properties obtained at the preceding step, adding a cryopreservative selected from the group consisting of polyethylene glycol, glycerol, and DMSO (dimethylsulfoxide).

11. Process for the preparation of isolated monocyte derived cells with immunostimulating properties comprising the steps: loading the monocyte derived cells obtained by claim 9 with an exogenous nucleic acid through endocytosis targeting their mannose and/or Fc receptors, or via pinocytosis of macromolecular nucleic acid aggregates, and submitting the monocyte derived cells obtained at the preceding step to physical stress including electropulsation from 1 to 10 pulses of 5 msecs at 0.3 to 1 kV/cm, enabling intracellular transfer of the exogenous nucleic acid into the nucleus and integration into the DNA of the nucleus.

12. Process for the preparation of isolated monocyte derived cells with immunostimulating properties comprising the steps: 1) recovering blood derived mononuclear cells directly from blood apheresis or from blood bag collection, followed by optional centrifugation, to eliminate a substantial part of red blood cells, granulocytes and platelets, and collection of peripheral blood leukocytes; 2) washing peripheral blood

leukocytes obtained at the preceding steps to obtain mononuclear cells; 3) resuspending the cells (monocytes+lymphocytes) obtained at the preceding step in culture medium (AIM-V, RPMI or IMDM type) at 106 to 2x107 cells/ml, possibly completed by cytokines and/or autologous serum, and culture for 5 to 10 days at 37° C. under O2/CO2 atmosphere in hydrophobic gas permeable bags, to obtain monocyte derived cells and contaminating lymphocytes; loading the monocyte derived cells thus obtained with an exogenous nucleic acid through endocytosis targeting their mannose and/or Fc receptors, or via pinocytosis of macromolecular nucleic acid aggregates, and submitting the monocyte derived cells obtained at the preceding step to electropulsation, enabling intracellular transfer of the exogenous nucleic acid into the nucleus and integration into the DNA of the nucleus.

13. Process for the preparation of isolated monocyte derived cells with immunostimulating properties according to claim 11, comprising, before the step of loading, the step of culturing said monocyte derived cells and contaminating lymphocytes for 2 to 24 hours, in the presence of drugs, proteins or antigens to interiorize these compounds in said monocyte derived cells.

14. Process for the preparation of isolated monocyte derived cells with immunostimulating properties according to claim 12, comprising the additional step of centrifuging the monocyte derived cells with immunostimulating properties at a temperature of 4° C., said temperature enabling cell preservation, and resuspending the cells in isotonic medium containing autologous serum.

15. Process for the preparation of isolated monocyte derived cells with immunostimulating properties according to claim 12, comprising the additional steps of: centrifuging the monocyte derived cells with immunostimulating properties at a temperature of 4° C., said temperature enabling cell preservation and resuspending the monocyte derived cells in isotonic medium containing autologous serum, and freezing at a temperature of at least -80° C. aliquots of the monocyte derived cells with immunostimulating properties obtained at the preceding step, with the addition of a cryopreservative selected from the group consisting of polyethylene glycol, glycerol, and DMSO (dimethyl-sulfoxide).

16. Pharmaceutical composition comprising, as active substance, isolated monocyte derived cells with immunostimulating properties according to claim 1, in association with a pharmaceutically acceptable vehicle.

17. Pharmaceutical composition according to claim 16, in the form of sterile injectable preparations or of sterile topical preparations.

18. Pharmaceutical composition in the form of a vaccine comprising, as active substance, isolated monocyte derived cells with immunostimulating properties according to claim 1, having integrated in their nucleus, an exogenous nucleic acid coding for a polypeptide or protein which is immunogenic.

19. Medicament comprising isolated monocyte derived cells with immunostimulating properties according to claim 1, in the form of a vaccine against tumors or infectious agents, and for treating polypeptide or protein deficiency in a patient.

L10 ANSWER 19 OF 21 USPATFULL on STN
2000:47089 Macrophages, process for preparing the same and their use as active

substances of pharmaceutical compositions.
Chokri, Mohamed, Deuil-la-Barre, France
Bartholeyns, Jacques, Bures-sur-Yvette, France
I.D.M. Immuno-Designed Molecules, Paris, France (non-U.S. corporation)
US 6051432 20000418
APPLICATION: US 1999-400875 19990922 (9)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A kit for producing compositions of autologous effector cells from selective extracts of human blood, comprising in combination: apparatus for cell washing, culture and purification; and chemical and biochemical reagents for cell culture and differentiation, a first said reagent for differentiation being GM-CSF.

2. The kit according to claim 1, wherein said apparatus for cell washing, culture and purification comprises at least one blood collection bag and devices for supplying reagents to said bag and withdrawing samples from said bag.

3. The kit according to claim 2, wherein said at least one blood collection bag is hydrophobic and non-adherent relative to macrophage compositions.

4. The kit according to claim 1, further comprising 1,25-dihydroxy vitamin D3 as a second said reagent for differentiation.

5. The kit according to claim 1, further comprising at least one activator of said autologous effector cells.

6. The kit according to claim 5, wherein said at least one activator is γ-interferon.

7. The kit according to claim 1, wherein a said reagent for cell culture is a modified IMDM.

8. The kit according to claim 7, wherein said modified IMDM contains ingredients selected from the group consisting of glutamine, pyruvic acid, indomethacin, cymetadine, mercaptoethanol, non-essential amino acids, and antibiotics.

9. The kit according to claim 1, wherein said apparatus for purification comprises an elutriator.

L10 ANSWER 20 OF 21 USPATFULL on STN
1999:163208 Macrophages, process for preparing the same and their use as active substances of pharmaceutical compositions.
Chokri, Mohamed, Deuil-la-Barre, France
Bartholeyns, Jacques, Bures-sur-Yvette, France
I.D.M. Immuno-Designed Molecules, Paris, France (non-U.S. corporation)
US 6001351 19991214
APPLICATION: US 1997-896498 19970718 (8)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. Macrophages having at least one of the following properties: their cytotoxic activity without IFN-γ is increased by about 20 to 30% with respect to standard macrophages; their cytotoxic activity with IFN-γ is increased by about 20 to about 40% with respect to standard macrophages; deactivations of the cytotoxic activity following activation of IFN-γ is such that sixty hours after activation with

IFN-γ, the residual cytotoxic activity is at least 30% of the maximum cytotoxic activity presented by the macrophages due to IFN-γ activation, with said cytotoxic activity being measured as a percentage of the inhibition of 3-H thymidine incorporation by target tumoral cells, particularly U 937 cells; said macrophages being prepared by culturing healthy human monocytes and lymphocytes in a culture medium containing 1,25-dihydroxy vitamin D3 and GM-CSF; said macrophages containing exogenous nucleic acids and/or drugs.

2. A method for treating cancer, comprising administering to a patient in need of said treatment an effective amount of the macrophages according to claim 1.

3. The method according to claim 2, wherein said effective amount is about 2x109 to about 5x109 macrophages.

4. The method according to claim 3, further comprising administering lymphocytes in an amount of about 4x109 to about 10x109 lymphocytes.

L10 ANSWER 21 OF 21 USPATFULL on STN
97:78173 Macrophages, process for preparing the same and their use as active substances of pharmaceutical compositions.
Chokri, Mohamed, Deuil-la-Barre, France
Bartholeyns, Jacques, Bures-sur-Yvette, France
I.D.M. Immuno-Designed Molecules, Paris, France (non-U.S. corporation)
US 5662899 19970902
WO 9426875 19941124
APPLICATION: US 1995-374629 19950117 (8)
WO 1993-EP1232 19930518 19950117 PCT 371 date 19950117 PCT 102(e) date
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. Macrophages having at least one of the following properties: their cytotoxic activity without IFN-γ is increased by about 20 to 30% with respect to standard macrophages; their cytotoxic activity with IFN-γ is increased by about 20 to about 40% with respect to standard macrophages; deactivation of the cytotoxic activity following activation of IFN-γ is such that sixty hours after activation with IFN-γ, the residual cytotoxic activity is at least 30% of the maximum cytotoxic activity presented by the macrophages due to IFN-γ activation, with said cytotoxic activity being measured as a percentage of the inhibition of 3-H thymidine incorporation by target tumoral cells, particularly U 937 cells; said macrophages being prepared by culturing healthy human monocytes and lymphocytes in a culture medium containing 1,25-dihydroxy vitamin D3 and GM-CSF.

2. Macrophages according to claim 1, having the following characteristics: their size is from about 10 to about 20 μm; they adhere to plastic surface; their viability is higher than about 70%; they present a phagocytosis property; they present on their surface antigens of differentiation selected from the group consisting of CD64, CD68, MAX1, and HLADR; their cytotoxic activity is higher than about 50%.

3. Process for preparing macrophages according to claim 1, comprising culturing monocytes in a culture medium containing 1,25-dihydroxy D3 vitamin and GM-CSF.

4. Process according to claim 3 comprising culturing both monocytes and lymphocytes in a culture medium containing 1,25-dihydroxy vitamin

D3 and GM-CSF for a time sufficient to obtain differentiated macrophages, activating the macrophages resulting from the monocytes and lymphocytes with IFN-γ, and separating the macrophages from the lymphocytes, before or after the activation with IFN-γ, and recovering the macrophages.

5. Process according to claim 3, wherein D3 vitamin is used at a concentration of 10-10 to about 10-7.

6. Process according to claim 3, wherein GM-CSF is used at a concentration of about 50 to about 1000 U/ml.

7. Process according to claim 3, wherein the culture medium is RPMI, IMDM, MEM, or DMEM.

8. Process according to claim 3, wherein the culture medium contains indomethacin or/and cimetidine.

9. Process according to claim 3, wherein the yield of macrophages is from about 40% to 76%.

10. Process according to claim 3, wherein killed tumoral cells are added into the culture medium simultaneously with macrophages, both cells coming from the same patient, at the ratio of about 1 million of killed tumoral cells/ml, with said tumoral cells being processed at the same time as macrophages.

11. Pharmaceutical compositions containing, as active substance macrophages according to claim 1.

12. Method for the treatment of cancer, comprising the administration of macrophages according to claim 1 in an amount from about 2x109 to 5x109 macrophages.

13. Method according to claim 12 for the treatment of cancer, comprising the administration of lymphocytes in an amount of about 4x109 to about 10x109 lymphocytes.

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L10  ANSWER 21 OF 21  USPATFULL on STN
EXNAM  Primary Examiner: Feisee, Lila; Assistant Examiner: Johnson, Nancy A.


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L1            2 S E4
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L2            2 S E3
L3            0 S L2 NOT L1
                E GARCIA LUIS/IN
L4           27 S E3-E5
L5           25 S L4 NOT L1
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L6             0 S L5 AND (MONOCYT? OR MACROPHAG? OR PHAGOCYT?)
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L9            23 S E4
L10           21 S L9 NOT L1

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                                                       ENTRY    SESSION
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=> d l11,bib,ab

L11  ANSWER 1 OF 1  WPIDS  COPYRIGHT 2006 THE THOMSON CORP on STN
Full Text
AN   1999-347126 [29]    WPIDS
DNN  N1999-259569        DNC C1999-102069
TI   Diagnosis and treatment of pathologies.
DC   B04 D16 S03
IN   BARTHOLEYNS, J; CHOKRI, M; DREYFUS, P A; GARCIA, L; PARRISH, E;
     PELTEKIAN, E
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PA (IDMI-N) IDM IMMUNO-DESIGNED MOLECULES; (INRM) INSERM INST NAT SANTE RECH MEDICALE; (BA P A; (GARC-I) GARCIA L; (PARR-I) PARRISH E; (PELT-I) PELTEKIAN E

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PI WO 9913054 A2 19990318 (199929)* EN 24
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AU 9894410 A 19990329 (199932)
EP 1009806 A2 20000621 (200033) EN
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
JP 2001515713 W 20010925 (200170) 34
US 2002068048 A1 20020606 (200241)
AU 752676 B 20020926 (200268)
US 2005048039 A1 20050303 (200517)

ADT WO 9913054 A2 WO 1998-EP5707 19980831; AU 9894410 A AU 1998-94410 19980831; EP 1009806 A2 EP 1998-947533 19980831, WO 1998-EP5707 19980831; JP 2001515713 W WO 1998-EP5707 19980831, JP 2000-510843 19980831; US 2002068048 A1 US 1997-924830 19970905; AU 752676 B AU 1998-94410 19980831; US 2005048039 A1 Div ex US 1997-924830 19970905, US 2004-766929 20040130

FDT AU 9894410 A Based on WO 9913054; EP 1009806 A2 Based on WO 9913054; JP 2001515713 W Based on WO 9913054; AU 752676 B Previous Publ. AU 9894410, Based on WO 9913054

PRAI US 1997-924830 19970905; US 2004-766929 20040130

AB WO 9913054 A UPAB: 19990723

NOVELTY - Diagnosis and treatment of pathologies comprises administration of exogenous monocyte derived cells loaded with corrective agents or a marker for detection is new.

DETAILED DESCRIPTION - Treatment or diagnosis of pathologies either expressed in injured or pathological multiple sites in tissues or in the body or expressed in injured or pathological sites of tissues or cells in sites of the body, which are difficult to access, with the sites or areas in immediate proximity to the sites being the source of the release of chemotactic factors for endogenous macrophages, either spontaneously or upon suitable stimulation, where the treatment is carried out by administration to the body of an appropriate amount of exogenous monocyte derived cells (MDCs). The MDCs are, in the case of treatment, loaded with corrective agents with respect to the pathologies to be treated. The MDCs also have the properties of mobilization towards the source of the released chemotactic factors and to target the cells present in the vicinity of the released chemotactic factors. In the case of diagnosis, the MDC's are loaded with a marker enabling the detection of injured or pathological sites.

INDEPENDENT CLAIMS are also included for the following:

(1) MDCs obtained by culturing blood mononuclear cells to obtain monocytes derived cargo cells, containing a therapeutic agent for a given pathology corresponding to loaded chemical or biological substances such as peptides, polypeptides, proteins and nucleic acids or virus or nucleic acids which have been transfected into the cells or these cells loaded externally on the membrane with emitting signals. The cells have one or more of the following properties:

(i) their preparation specifically induce an increased membrane expression level of chemotactic receptors;

(ii) they are sensitive, particularly in vivo, to chemotactic factors released by sites of call or suffering cells;

(iii) they have membrane plasticity such that they can enter difficult injured sites to access such as the central nervous system (CNS);

(iv) they can rapidly reach sites of call, as soon as 2 hours to 3 days, particularly 2 to 3 days after systemic injection;

(v) they can accumulate into injured sites of call;

(vi) they remain alive in the vicinity of the injured or pathological sites for several months, particularly at least up to about 4 months;

(vii) their morphology becomes similar to the morphology of the cells normally present in the injured sites or pathological sites and they integrate the tissue cells of the injured or pathological sites; and

(viii) they can release the contained corrective agent in the sites of call, either constitutively or on demand by induction of secretion of the corrective agent;

(2) a kit for the preparation of MDCs as in (1) comprising:

(a) a culture device (bags and reagents) for the maturation of mononuclear cells into phagocytes, particularly macrophages;

(b) therapeutic agents to be introduced into the phagocytes and a device for introducing them to obtain MDCs.

USE - The method can be used for the treatment of pathologies particularly having multiple expressed sites resulting from disseminated cancers or from inflammatory diseases (claimed). Pathologies which may be treated by the method include:

(1) for the central nervous system (CNS): genetic diseases (e.g. adrenoleukodystrophy, spinal muscular atrophy, Gauchers disease and Huntingtons disease), and sporadic diseases (e.g. Alzheimers disease, Parikinsons disease, amyotrophic lateral sclerosis, multiple sclerosis, strokes, glioblastoma, cerebral metastasis, infection of the CNS); and

(2) for the peripheral nervous and muscular system: genetic diseases (e.g. Duchenne disease, Becker's disease, muscular dystrophies), non genetic diseases (e.g. neuropathies and muscular necrosis from different origins including trauma), rheumatoid arthritis, atheromatosis, bone trauma or bone infection or degenerescence and pulmonary fibrosis (claimed).

Dwg.0/4

```
=> e parrish e/in
E1            1     PARRISH D S/IN
E2            1     PARRISH D W/IN
E3            1 --> PARRISH E/IN
E4            1     PARRISH E J/IN
E5            2     PARRISH E S/IN
E6            7     PARRISH F/IN
E7            1     PARRISH F A/IN
E8            1     PARRISH F B/IN
E9            1     PARRISH F C/IN
E10           1     PARRISH F W/IN
E11          11     PARRISH G C/IN
E12           1     PARRISH G F/IN

=> s e3
L12           1 "PARRISH E"/IN

=> s l12 not l11
L13           0 L12 NOT L11

=> e garcia l/in
E1            1     GARCIA K P/IN
E2            1     GARCIA K R/IN
E3           40 --> GARCIA L/IN
E4            7     GARCIA L A/IN
E5            1     GARCIA L A F/IN
E6            1     GARCIA L A M/IN
E7            1     GARCIA L A R/IN
E8            1     GARCIA L A R G/IN
E9            1     GARCIA L B/IN
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E10          14     GARCIA L C/IN
E11           1     GARCIA L E/IN
E12           2     GARCIA L F/IN

=> s e3
L14          40 "GARCIA L"/IN

=> s l14 and (monocyt? or macrophage or phagocyt?)
          3889 MONOCYT?
          4093 MACROPHAGE
          1281 PHAGOCYT?
L15           1 L14 AND (MONOCYT? OR MACROPHAGE OR PHAGOCYT?)

=> d l15,bib,ab

L15  ANSWER 1 OF 1  WPIDS  COPYRIGHT 2006 THE THOMSON CORP on STN
Full Text
AN   1999-347126 [29]   WPIDS
DNN  N1999-259569       DNC C1999-102069
TI   Diagnosis and treatment of pathologies.
DC   B04 D16 S03
IN   BARTHOLEYNS, J; CHOKRI, M; DREYFUS, P A; GARCIA, L; PARRISH, E;
     PELTEKIAN, E
PA   (IDMI-N) IDM IMMUNO-DESIGNED MOLECULES; (INRM) INSERM INST NAT SANTE      RECH MEDICALE; (B
     P A; (GARC-I) GARCIA L; (PARR-I) PARRISH E; (PELT-I) PELTEKIAN E
CYC  83
PI   WO 9913054      A2 19990318 (199929)* EN   24
        RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL
            OA PT SD SE SZ UG ZW
         W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE
            GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG
            MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG
            US UZ VN YU ZW
     AU 9894410      A  19990329 (199932)
     EP 1009806      A2 20000621 (200033)  EN
         R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
     JP 2001515713   W  20010925 (200170)       34
     US 2002068048   A1 20020606 (200241)
     AU 752676       B  20020926 (200268)
     US 2005048039   A1 20050303 (200517)
ADT  WO 9913054 A2 WO 1998-EP5707 19980831; AU 9894410 A AU 1998-94410
     19980831; EP 1009806 A2 EP 1998-947533 19980831, WO 1998-EP5707 19980831;
     JP 2001515713 W WO 1998-EP5707 19980831, JP 2000-510843 19980831; US
     2002068048 A1 US 1997-924830 19970905; AU 752676 B AU 1998-94410 19980831;
     US 2005048039 A1 Div ex US 1997-924830 19970905, US 2004-766929 20040130
FDT  AU 9894410 A Based on WO 9913054; EP 1009806 A2 Based on WO 9913054; JP
     2001515713 W Based on WO 9913054; AU 752676 B Previous Publ. AU 9894410,
     Based on WO 9913054
PRAI US 1997-924830       19970905; US 2004-766929       20040130
AB   WO   9913054 A UPAB: 19990723
     NOVELTY - Diagnosis and treatment of pathologies comprises administration
     of exogenous monocyte derived cells loaded with corrective agents or a
     marker for detection is new.
          DETAILED DESCRIPTION - Treatment or diagnosis of pathologies either
     expressed in injured or pathological multiple sites in tissues or in the
     body or expressed in injured or pathological sites of tissues or cells in
     sites of the body, which are difficult to access, with the sites or areas
     in immediate proximity to the sites being the source of the release of
     chemotactic factors for endogenous macrophages, either spontaneously or
     upon suitable stimulation, where the treatment is carried out by
     administration to the body of an appropriate amount of exogenous
     monocyte derived cells (MDCs). The MDCs are, in the case of treatment,
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loaded with corrective agents with respect to the pathologies to be treated. The MDCs also have the properties of mobilization towards the source of the released chemotactic factors and to target the cells present in the vicinity of the released chemotactic factors. In the case of diagnosis, the MDC's are loaded with a marker enabling the detection of injured or pathological sites.

INDEPENDENT CLAIMS are also included for the following:

(1) MDCs obtained by culturing blood mononuclear cells to obtain **monocytes** derived cargo cells, containing a therapeutic agent for a given pathology corresponding to loaded chemical or biological substances such as peptides, polypeptides, proteins and nucleic acids or virus or nucleic acids which have been transfected into the cells or these cells loaded externally on the membrane with emitting signals. The cells have one or more of the following properties:

(i) their preparation specifically induce an increased membrane expression level of chemotactic receptors;

(ii) they are sensitive, particularly in vivo, to chemotactic factors released by sites of call or suffering cells;

(iii) they have membrane plasticity such that they can enter difficult injured sites to access such as the central nervous system (CNS);

(iv) they can rapidly reach sites of call, as soon as 2 hours to 3 days, particularly 2 to 3 days after systemic injection;

(v) they can accumulate into injured sites of call;

(vi) they remain alive in the vicinity of the injured or pathological sites for several months, particularly at least up to about 4 months;

(vii) their morphology becomes similar to the morphology of the cells normally present in the injured sites or pathological sites and they integrate the tissue cells of the injured or pathological sites; and

(viii) they can release the contained corrective agent in the sites of call, either constitutively or on demand by induction of secretion of the corrective agent;

(2) a kit for the preparation of MDCs as in (1) comprising:

(a) a culture device (bags and reagents) for the maturation of mononuclear cells into **phagocytes**, particularly macrophages;

(b) therapeutic agents to be introduced into the **phagocytes** and a device for introducing them to obtain MDCs.

USE - The method can be used for the treatment of pathologies particularly having multiple expressed sites resulting from disseminated cancers or from inflammatory diseases (claimed). Pathologies which may be treated by the method include:

(1) for the central nervous system (CNS): genetic diseases (e.g. adrenoleukodystrophy, spinal muscular atrophy, Gauchers disease and Huntingtons disease), and sporadic diseases (e.g. Alzheimers disease, Parikinsons disease, amyotrophic lateral sclerosis, multiple sclerosis, strokes, glioblastoma, cerebral metastasis, infection of the CNS); and

(2) for the peripheral nervous and muscular system: genetic diseases (e.g. Duchenne disease, Becker's disease, muscular dystrophies), non genetic diseases (e.g. neuropathies and muscular necrosis from different origins including trauma), rheumatoid arthritis, atheromatosis, bone trauma or bone infection or degenerescence and pulmonary fibrosis (claimed).

Dwg.0/4

```
=> e peltekian e/in
E1          20     PELTEK V V/IN
E2           2     PELTEKIAN A M/IN
E3           2 --> PELTEKIAN E/IN
E4           1     PELTEKOVA V D/IN
E5           1     PELTENBURG H G/IN
E6           1     PELTENBURG W/IN
```

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E7            1      PELTENBURG W K M/IN
E8            1      PELTENKO V I/IN
E9            4      PELTER A/IN
E10           1      PELTER J M/IN
E11           1      PELTERS R/IN
E12           7      PELTERS S/IN

=> s e3
L16           2 "PELTEKIAN E"/IN

=> d his

     (FILE 'HOME' ENTERED AT 16:51:29 ON 28 SEP 2006)

     FILE 'USPATFULL' ENTERED AT 16:51:54 ON 28 SEP 2006
                 E DREYFUS P A/IN
L1             2 S E4
                 E PARRISH ELAINE/IN
L2             2 S E3
L3             0 S L2 NOT L1
                 E GARCIA LUIS/IN
L4            27 S E3-E5
L5            25 S L4 NOT L1
L6             0 S L5 AND (MONOCYT? OR MACROPHAG? OR PHAGOCYT?)
                 E PELTEKIAN ELISE/IN
L7             3 S E3
L8             1 S L7 NOT L1
                 E BARTHOLEYNS JACQUE/IN
L9            23 S E4
L10           21 S L9 NOT L1

     FILE 'WPIDS' ENTERED AT 16:59:22 ON 28 SEP 2006
                 E DREYFUS P A/IN
L11            1 S E3
                 E PARRISH E/IN
L12            1 S E3
L13            0 S L12 NOT L11
                 E GARCIA L/IN
L14           40 S E3
L15            1 S L14 AND (MONOCYT? OR MACROPHAGE OR PHAGOCYT?)
                 E PELTEKIAN E/IN
L16            2 S E3

=> s l16 not l11
L17           1 L16 NOT L11

=> d l17,bib,ab,

L17  ANSWER 1 OF 1  WPIDS  COPYRIGHT 2006 THE THOMSON CORP on STN
Full Text
AN   2001-381700 [40]   WPIDS
DNC  C2001-116988
TI   Canine adenovirus vector for gene transfer, is obtained by co-transforming
     Escherichia coli cell with first and pre-transfer plasmids, transfecting
     recombinant vector into host cell and recovering adenoviral particle.
DC   B04 D16
IN   BOUTIN, S; CHILLON, R M; DANOS, O; GARCIA, L; KREMER, E; PELTEKIAN, E;
     SOUDAIS, C; VINCENT, N; CHILLON RODRIGUEZ, M
PA   (GENE-N) GENETHON III; (INRM) INSERM INST NAT SANTE RECH MEDICALE;
     (BOUT-I) BOUTIN S; (RODR-I) CHILLON RODRIGUEZ M; (DANO-I) DANOS O;
     (GARC-I) GARCIA L; (KREM-I) KREMER E; (PELT-I) PELTEKIAN E; (SOUD-I)
     SOUDAIS C; (VINC-I) VINCENT N; (INRM) INST NAT SANTE RECH MEDICALE
```

CYC 29
PI WO 2001042481 A2 20010614 (200140)* EN 107
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR
W: CA JP US
EP 1118670 A1 20010725 (200143) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
EP 1248851 A2 20021016 (200276) EN
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE TR
US 2003100116 A1 20030529 (200337)
ADT WO 2001042481 A2 WO 2000-EP12792 20001206; EP 1118670 A1 EP 1999-403061 19991207; EP 1248851 A2 EP 2000-990766 20001206, WO 2000-EP12792 20001206; US 2003100116 A1 Cont of WO 2000-EP12792 20001206, US 2002-165202 20020607
FDT EP 1248851 A2 Based on WO 2001042481
PRAI EP 1999-403078 19991208; EP 1999-403061 19991207
AB WO 200142481 A UPAB: 20010719
NOVELTY - Canine adenovirus (CAV) vector (I), obtained by co-transforming Escherichia coli cells having recBC sbcBC phenotype by a first plasmid and a pre-transfer plasmid for their homologous recombination, isolating DNA fragment comprising recombinant vector genome (II), transfecting DK28Cre cells (CNCM I-2293) that transcomplement (II), recovering and purifying the produced adenoviral particles, is new.

DETAILED DESCRIPTION - (I) is obtainable by a method (M) which involves co-transforming E.coli cells having recBC sbcBC phenotype by a first plasmid and a pre-transfer plasmid in conditions enabling their homologous recombination, in order to generate a transfer plasmid devoid of a functional E1 coding region, comprising the desired recombinant vector genome, where the first plasmid comprises the Inverted Terminal Regions (ITR) and the packaging signal (psi) sequences of a CAV genome, and the pre-transfer plasmid includes the sequence whose insertion in the vector genome is desired, flanked by sequences homologous to sequences of the first plasmid surrounding the region of the first plasmid where the modification is desired, isolating a DNA fragment essentially comprising (II) by enzyme restriction, transfecting DK28Cre cells (CNCM I-2293) that are rendered capable to transcomplement (II), and recovering and purifying the recombinant adenoviral particles produced.

INDEPENDENT CLAIMS are also included for the following:

(1) CAV vector comprising a nucleotide sequence derived from CAV-2 strain Toronto A26/61 genomic sequence being devoid of the E1 region of the CAV genome, comprising the left and right ITR sequences and the packaging signal (psi) sequence, and an expression cassette comprising a nucleotide sequence to be transferred in target cells which is under the control of regulation sequences including a promoter sequence;

(2) CAV helper vector (II) derived from (I) and further comprising lox sequences inserted in positions of the CAV genome which allow the deletion of the psi sequence of the CAV genome, when the vector is contacted with a Cre recombinase;

(3) CAV vector genome (III) such as that comprised in (I);

(4) a DNA construct (IV) comprising (III);

(5) plasmid pEJK25, p25GFP, pCAVGFP or pCAVBFP, comprising (III);

(6) transcomplementing cell line (V) for the production of CAV vector particles, which is a Dog Kidney (DK) cell line stably expressing the E1 region of the genomic sequence of a CAV-2 Manhattan strain (deposited at the CNCM on August 16, 1999, under no. I-2291);

(7) CAV vector preparation that contains more than 1013 viral particles/ml that is contaminated by less than 1 replication-competent particle in 2.1011 viral particles;

(8) generating recombinant CAV particles, and gutless CAV vectors, by (M);

(9) a kit for the generation of recombinant CAV, comprising (V), a first plasmid devoid of the E1 coding region of the CAV genome, a pre-transfer plasmid, including sequences homologous to sequences of the

first plasmid flanking the E1 deletion and E.coli cells; and
(10) a kit for the generation of gutless CAV vectors, comprising (V), first plasmid devoid of all the viral coding sequences of the CAV genome, a pre-transfer plasmid including sequences homologous to sequences of the first plasmid, and E.coli cells.
ACTIVITY - None given.
MECHANISM OF ACTION - Gene therapy; vaccine.
No supporting data given.
USE - (I) and (III) are useful for the preparation of a therapeutic composition for the treatment or modification of neuronal cells, for the targeted administration of a nucleotide sequence of therapeutic interest in neuronal cells, for the preparation of therapeutic composition capable of specifically interacting with neuritic terminations, for the transfer of a nucleotide sequence of interest in vivo in neuronal cells, for the treatment of a human patient presenting a humoral immunity against human adenovirus, and for the screening of the delivery of a nucleotide sequence of interest in neuronal cells. (V) is useful for the production of a CAV vector (claimed).
ADVANTAGE - The method is suitable for producing improved CAV vectors that have recourse to different means, for instance in choosing a type of CAV strain, and/or selecting particular cell lines for transcomplementing of vector genome in order to produce stocks of vectors.
Dwg.0/39

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=> file medline
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                    32.93      99.30

FILE 'MEDLINE' ENTERED AT 17:02:36 ON 28 SEP 2006

 FILE LAST UPDATED: 27 Sep 2006 (20060927/UP). FILE COVERS 1950 TO DATE.

 On December 11, 2005, the 2006 MeSH terms were loaded.

 The MEDLINE reload for 2006 is now (26 Feb.) available. For details
 on the 2006 reload, enter HELP RLOAD at an arrow prompt (=>).
 See also:

    http://www.nlm.nih.gov/mesh/
    http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html
    http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_med_data_changes.html
    http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_2006_MeSH.html

 OLDMEDLINE is covered back to 1950.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2006 vocabulary.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> e dreyfus p a/au
E1            2     DREYFUS N G/AU
E2          115     DREYFUS P/AU
E3           18 --> DREYFUS P A/AU
E4            1     DREYFUS P C/AU
E5           42     DREYFUS P M/AU
E6            1     DREYFUS PATRICK/AU
E7            4     DREYFUS PATRICK A/AU
E8            9     DREYFUS R/AU
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E9            1     DREYFUS R A B/AU
E10           2     DREYFUS R H/AU
E11           2     DREYFUS REMI/AU
E12           1     DREYFUS RUTH/AU

=> s e2 or e3
           115 "DREYFUS P"/AU
            18 "DREYFUS P A"/AU
L18        133 "DREYFUS P"/AU OR "DREYFUS P A"/AU

=> s l18 and (monocyt? or macrophag? or phagocyt?)
         82778 MONOCYT?
        154580 MACROPHAG?
         61504 PHAGOCYT?
L19          3 L18 AND (MONOCYT? OR MACROPHAG? OR PHAGOCYT?)

=> d l19,ti,1-3

L19  ANSWER 1 OF 3     MEDLINE on STN
TI   Macrophagic myofasciitis lesions assess long-term persistence of
     vaccine-derived aluminium hydroxide in muscle.

L19  ANSWER 2 OF 3     MEDLINE on STN
TI   Differential microglial response to progressive neurodegeneration in the
     murine mutant Wobbler.

L19  ANSWER 3 OF 3     MEDLINE on STN
TI   Targeting widespread sites of damage in dystrophic muscle: engrafted
     macrophages as potential shuttles.


=> d l19,cbib,ab,3

L19  ANSWER 3 OF 3     MEDLINE on STN
97083333.    PubMed ID: 8929907.   Targeting widespread sites of damage in
     dystrophic muscle: engrafted macrophages as potential shuttles. Parrish
     E P; Cifuentes-Diaz C; Li Z L; Vicart P; Paulin D; Dreyfus P A;
     Peschanski M; Harris A J; Garcia L. (Neuroplasticite et Therapeutique,
     INSERM U421, Faculte de Medicine, France. ) Gene therapy, (1996 Jan) Vol.
     3, No. 1, pp. 13-20.  Journal code: 9421525. ISSN: 0969-7128. Pub.
     country: ENGLAND: United Kingdom. Language: English.
AB   Inherited muscle diseases are characterized by widespread muscle damage in
     the body.  This limits the clinical relevance of cell or gene therapy
     based upon direct injections into muscles.  One way to circumvent this
     obstacle would be to use circulating cells, capable of homing naturally to
     the sites of lesion, to deliver therapeutic substances.  Certain muscular
     dystrophies present successive cycles of degeneration-regeneration.  These
     sporadic necrotic lesions trigger local inflammations with subsequent
     infiltration of blood-borne mononuclear cells.  We have, therefore, tested
     the possibility that homing monocytes and macrophages could be
     appropriate shuttles for delivering a therapeutic agent to disseminated
     pathogenic sites, their targeting being triggered by the pathogeny itself.
     First, fluorescently labeled immortalized monocytes were intravenously
     injected into mice which had previously undergone freeze-damaging of
     individual muscles.  In agreement with our hypothesis, intense labelling
     was observed in the muscle, specifically in damaged regions.  Second, the
     technique was adapted to meet the needs of chronic diseases with
     characteristic continuous, widespread degeneration of muscle fibers, by
     creating a reservoir of genetically engineered monocytes, via bone
     marrow transplantation.  Mdx mice received bone marrow from transgenic
     mice expressing the lacZ reporter gene, under the control of the vimentin
     promoter, which is active in monocytes and macrophages.  Histological
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and molecular analyses demonstrated the homing of engineered **macrophages** at the sites of muscle damage, for periods as long as 2 months. Bone marrow progenitor cells, appropriately engineered to elicit the synthesis, in **macrophages**, of therapeutically relevant substances, may be of clinical value in various pathologies involving an inflammatory phase.

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=> d his

     (FILE 'HOME' ENTERED AT 16:51:29 ON 28 SEP 2006)

     FILE 'USPATFULL' ENTERED AT 16:51:54 ON 28 SEP 2006
                E DREYFUS P A/IN
L1            2 S E4
                E PARRISH ELAINE/IN
L2            2 S E3
L3            0 S L2 NOT L1
                E GARCIA LUIS/IN
L4           27 S E3-E5
L5           25 S L4 NOT L1
L6            0 S L5 AND (MONOCYT? OR MACROPHAG? OR PHAGOCYT?)
                E PELTEKIAN ELISE/IN
L7            3 S E3
L8            1 S L7 NOT L1
                E BARTHOLEYNS JACQUE/IN
L9           23 S E4
L10          21 S L9 NOT L1

     FILE 'WPIDS' ENTERED AT 16:59:22 ON 28 SEP 2006
                E DREYFUS P A/IN
L11           1 S E3
                E PARRISH E/IN
L12           1 S E3
L13           0 S L12 NOT L11
                E GARCIA L/IN
L14          40 S E3
L15           1 S L14 AND (MONOCYT? OR MACROPHAGE OR PHAGOCYT?)
                E PELTEKIAN E/IN
L16           2 S E3
L17           1 S L16 NOT L11

     FILE 'MEDLINE' ENTERED AT 17:02:36 ON 28 SEP 2006
                E DREYFUS P A/AU
L18         133 S E2 OR E3
L19           3 S L18 AND (MONOCYT? OR MACROPHAG? OR PHAGOCYT?)

=> d l18,ti,1-10

L18  ANSWER 1 OF 133      MEDLINE on STN
TI   Expression of vesicular glutamate transporters, VGLUT1 and VGLUT2, in
     cholinergic spinal motoneurons.

L18  ANSWER 2 OF 133      MEDLINE on STN
TI   [Stem cells and neuromuscular disease].
     Cellules souches et maladies neuromusculaires.

L18  ANSWER 3 OF 133      MEDLINE on STN
TI   Muscle precursor cell autografting in a murine model of urethral sphincter
     injury.

L18  ANSWER 4 OF 133      MEDLINE on STN
TI   Oligoclonal T-cells in blood and target tissues of patients with anti-Hu
```

syndrome.

L18 ANSWER 5 OF 133 MEDLINE on STN
TI Macrophagic myofasciitis lesions assess long-term persistence of vaccine-derived aluminium hydroxide in muscle.

L18 ANSWER 6 OF 133 MEDLINE on STN
TI Differential microglial response to progressive neurodegeneration in the murine mutant Wobbler.

L18 ANSWER 7 OF 133 MEDLINE on STN
TI Ciliary neurotrophic factor may activate mature astrocytes via binding with the leukemia inhibitory factor receptor.

L18 ANSWER 8 OF 133 MEDLINE on STN
TI Angiotensin II induces nuclear factor- kappa B activation in cultured neonatal rat cardiomyocytes through protein kinase C signaling pathway.

L18 ANSWER 9 OF 133 MEDLINE on STN
TI Altered balance between matrix gelatinases (MMP-2 and MMP-9) and their tissue inhibitors in human dilated cardiomyopathy: potential role of MMP-9 in myosin-heavy chain degradation.

L18 ANSWER 10 OF 133 MEDLINE on STN
TI Peripheral injections of Freund's adjuvant in mice provoke leakage of serum proteins through the blood-brain barrier without inducing reactive gliosis.

=> d l18,ti,11-133

L18 ANSWER 11 OF 133 MEDLINE on STN
TI Heart and lung VEGF mRNA expression in rats with monocrotaline- or hypoxia-induced pulmonary hypertension.

L18 ANSWER 12 OF 133 MEDLINE on STN
TI Regulation of growth factor gene expression in degenerating motoneurons of the murine mutant wobbler: a cellular patch-sampling/RT-PCR study.

L18 ANSWER 13 OF 133 MEDLINE on STN
TI Abducens palsy after an intrathecal glucocorticoid injection. Evidence for a role of intracranial hypotension.

L18 ANSWER 14 OF 133 MEDLINE on STN
TI Phenotypic alteration of astrocytes induced by ciliary neurotrophic factor in the intact adult brain, As revealed by adenovirus-mediated gene transfer.

L18 ANSWER 15 OF 133 MEDLINE on STN
TI Transforming growth factor alpha expression as a response of murine motor neurons to axonal injury and mutation-induced degeneration.

L18 ANSWER 16 OF 133 MEDLINE on STN
TI Magnetic resonance angiographic analysis of atlanto-axial rotation: anatomic bases of compression of the vertebral arteries.

L18 ANSWER 17 OF 133 MEDLINE on STN
TI Targeting widespread sites of damage in dystrophic muscle: engrafted macrophages as potential shuttles.

L18 ANSWER 18 OF 133 MEDLINE on STN
TI Bcl-2 sensitivity differentiates two pathways for motoneuronal death in

the wobbler mutant mouse.

L18 ANSWER 19 OF 133 MEDLINE on STN
TI Short increase of BDNF messenger RNA triggers kainic acid-induced neuronal hypertrophy in adult mice.

L18 ANSWER 20 OF 133 MEDLINE on STN
TI The mouse mutation muscle deficient (mdf) is characterized by a progressive motoneuron disease.

L18 ANSWER 21 OF 133 MEDLINE on STN
TI Early detection of mouse wobbler mutation: a model of pathological motoneurone death.

L18 ANSWER 22 OF 133 MEDLINE on STN
TI Transforming growth factor alpha (TGF alpha) expression in degenerating motoneurons of the murine mutant wobbler: a neuronal signal for astrogliosis?.

L18 ANSWER 23 OF 133 MEDLINE on STN
TI Rotation of the cervical spinal column: a computed tomography in vivo study.

L18 ANSWER 24 OF 133 MEDLINE on STN
TI Definition, at the molecular level, of a thyroglobulin-acetylcholinesterase shared epitope: study of its pathophysiological significance in patients with Graves' ophthalmopathy.

L18 ANSWER 25 OF 133 MEDLINE on STN
TI Rheumatic manifestations in a patient with human immunodeficiency virus type 2 infection.

L18 ANSWER 26 OF 133 MEDLINE on STN
TI Phosphatidylinositol is involved in the attachment of tailed asymmetric acetylcholinesterase to neuronal membranes.

L18 ANSWER 27 OF 133 MEDLINE on STN
TI Phenotypic and functional reversion of muscular dysgenesis by heterotypic fibroblast-myotube fusion in vitro.

L18 ANSWER 28 OF 133 MEDLINE on STN
TI Tissue-specific processing and polarized compartmentalization of clone-produced cholinesterase in microinjected Xenopus oocytes.

L18 ANSWER 29 OF 133 MEDLINE on STN
TI Expression and tissue-specific assembly of human butyrylcholine esterase in microinjected Xenopus laevis oocytes.

L18 ANSWER 30 OF 133 MEDLINE on STN
TI De novo amplification within a "silent" human cholinesterase gene in a family subjected to prolonged exposure to organophosphorous insecticides.

L18 ANSWER 31 OF 133 MEDLINE on STN
TI Cross-homologies and structural differences between human cholinesterases revealed by antibodies against cDNA-produced human butyrylcholinesterase peptides.

L18 ANSWER 32 OF 133 MEDLINE on STN
TI Genetic and pharmacological models of muscle inactivity.

L18 ANSWER 33 OF 133 MEDLINE on STN
TI The voltage-dependent sodium channel is co-localized with the

acetylcholine receptor at the vertebrate neuromuscular junction.

L18 ANSWER 34 OF 133 MEDLINE on STN
TI [Burkitt's disease. Apropos of apparently surgical forms].
La maladie de Burkitt. A propos des formes apparemment chirurgicales.

L18 ANSWER 35 OF 133 MEDLINE on STN
TI [Complex urogenital fistula surgically treated in the 2 University Hospital Centers of Abidjan. Value of viscero- and parietoplasties. Apropos of 1018 cases].
Fistules urogenitales complexes operees dans les deux C.H.U. d'Abidjan: de l'interet des viscero et parieto-plasties. A propos de 1018 cas.

L18 ANSWER 36 OF 133 MEDLINE on STN
TI [Rheumatological manifestations of adrenal insufficiencies].
Manifestations rhumatologiques des insuffisances surrenales.

L18 ANSWER 37 OF 133 MEDLINE on STN
TI [Joint manifestations and Yersinia pseudotuberculosis. Correlation between the clinical and biological aspects].
Manifestations articulaires et Yersinia pseudotuberculosis. Confrontation de la clinique et de la biologie.

L18 ANSWER 38 OF 133 MEDLINE on STN
TI Polymorphism of acetylcholinesterase and identification of new molecular forms after sedimentation analysis.

L18 ANSWER 39 OF 133 MEDLINE on STN
TI [Arthritis caused by sea urchin spine. Apropos of 2 new cases].
Les arthrites a piquants d'oursin. A propos de deux nouveaux cas.

L18 ANSWER 40 OF 133 MEDLINE on STN
TI [Study of HLA antigens A and B and their cross reactions in B27-negative ankylosing spondylarthritis].
Etude des antigenes HLA A et B et de leurs reactions croisees dans la spondylarthrite ankylosante B27 negative.

L18 ANSWER 41 OF 133 MEDLINE on STN
TI [Cross reactions of HLA A and B antigens in 63 patients with rheumatoid arthritis].
Etude des reactions croisees des antigenes HLA A et B chez 63 patients atteints de polyarthrite rhumatoide.

L18 ANSWER 42 OF 133 MEDLINE on STN
TI [Meralgia paresthetica complicating iliac bone graft removal. Apropos of 3 cases].
Meralgie paresthesique compliquant le prelevement d'un greffon iliaque. A propos de 3 observations [lettre].

L18 ANSWER 43 OF 133 MEDLINE on STN
TI Distribution and quantification of ACh receptors and innervation in diaphragm muscle of normal and mdg mouse embryos.

L18 ANSWER 44 OF 133 MEDLINE on STN
TI Acetylcholinesterase of mammalian neuromuscular junctions: presence of tailed asymmetric acetylcholinesterase in synaptic basal lamina and sarcolemma.

L18 ANSWER 45 OF 133 MEDLINE on STN
TI [Acetylcholinesterase and butyrylcholinesterase in mouse skeletal muscle. Specificity of irreversible inhibition by an organophosphorus compound of the methylphosphorothiolate type and multiple molecular forms].

Acetylcholinesterase et butyrylcholinesterase dans le muscle squelettique de souris. Specificite d'inhibition irreversible par un compose organophosphore de type methylphosphorothiolate et formes moleculaires multiples.

L18 ANSWER 46 OF 133 MEDLINE on STN
TI [Sea urchin spines synovitis. A case report with positive pasteurellosis antigen intradermoreaction (author's transl)].
Arthrites a piquants d'oursin. Un cas avec intradermoreaction positive a l'antigene pasteurellien.

L18 ANSWER 47 OF 133 MEDLINE on STN
TI [Rheumatoid nodulitis. Apropos of a case. Review of the literature].
La nodulite rhumatoide. A propos d'un cas - Revue de la litterature.

L18 ANSWER 48 OF 133 MEDLINE on STN
TI [Synovitis caused by stings. Apropos of a case associating synovitis caused by sea urchin stings and pasteurellosis].
Les synovites a piquants. A propos d'un cas associant une synovite a piquants d'oursins et une pasteurellose.

L18 ANSWER 49 OF 133 MEDLINE on STN
TI [Acroparesthesia of the arms].
Les acroparesthesies des membres superieurs.

L18 ANSWER 50 OF 133 MEDLINE on STN
TI [Synovitis caused by a sea-urchin sting associated with an inoculation pasteurella infection].
Synovite a piquant d'oursins associee a une inoculation pasteurellienne.

L18 ANSWER 51 OF 133 MEDLINE on STN
TI [Medico legal compensation of post-traumatic rheumatoid mono or.polyarthritides].
Reparation medico-legale des mono-ou polyarthrites rhumatoides post-traumatiques.

L18 ANSWER 52 OF 133 MEDLINE on STN
TI The effect of high doses of vitamin B6 on autistic children: a double-blind crossover study.

L18 ANSWER 53 OF 133 MEDLINE on STN
TI [Treatment of mycotic disorders].
Traitement des affections mycosiques.

L18 ANSWER 54 OF 133 MEDLINE on STN
TI [Acroparesthesias of the arm (author's transl)].
Die Akroparasthesien des Arms.

L18 ANSWER 55 OF 133 MEDLINE on STN
TI [Neuromuscular junction. History and present-day knowledge].
La jonction neuro-musculaire. Historie et actualite.

L18 ANSWER 56 OF 133 MEDLINE on STN
TI [Giant exogastric schwannoma (diagnostic and therapeutic considerations on a case)].
Schwannome geant exogastrique (considerations diagnostiques et therapeutiques; a propos d'une observation).

L18 ANSWER 57 OF 133 MEDLINE on STN
TI [Acroparesthesia of the upper limbs. Basis of the disorder. Symptomatology of carpal acroparesthesias].
Le acroparestesie degli arti superiori. Impostazione del disturbo.

Semeiologia delle acroparestesie carpali.

L18 ANSWER 58 OF 133 MEDLINE on STN
TI [Identification of acetate as the precursor of the acetyl moity of acetylcholine in neuromuscular junctions of the rat].
Identification de l'acetate comme precurseur du radical acetyl de l'acetylcholine des jonctions neuro-musculaires du Rat.

L18 ANSWER 59 OF 133 MEDLINE on STN
TI [Stereological study on the frequency of hepatic giant mitochondria in patients with Gilbert's disease as compared with a normal control group (author's transl)].
Etude stereologique de la frequence des mitochondries geantes hepatiques dans la maladie de Gilbert. Comparaison avec le sujet normal.

L18 ANSWER 60 OF 133 MEDLINE on STN
TI Histochemical and ultrastructural study of muscle biopsies in 3 cases of dystrophia myotonica in the newborn child.

L18 ANSWER 61 OF 133 MEDLINE on STN
TI [Osteomalacia, intestinal malabsorption, polyadenopathy and inflammatory polyarthritis due to stagnant loop syndrome].
Osteomalacie, malabsorption intestinale, polyadenopathies et polyarthrite inflammatoire par phenomene d'anse stagnante.

L18 ANSWER 62 OF 133 MEDLINE on STN
TI [Dorsal herniated disc].
La hernie discale dorsale.

L18 ANSWER 63 OF 133 MEDLINE on STN
TI [Complications in the region of skull and neck in car accidents (whiplash syndrome)].
Komplikationen im Schadel-Hals-Bereich bei Autounfallen (Das Schleudertrauma-Syndrom.

L18 ANSWER 64 OF 133 MEDLINE on STN
TI [Arthroscopy of the knee joint. Methods and results].
Arthroskopie des Kniegelenkes. Methoden und Ergebnisse.

L18 ANSWER 65 OF 133 MEDLINE on STN
TI [Cervico-cephalic complications of automobile accidents. The posttraumatic cervical-cephalic syndrome].
Complicaciones cervico-cefalicas de los accidentes de automovil. El sindrome cervico-cefalico post-traumatico.

L18 ANSWER 66 OF 133 MEDLINE on STN
TI [Arthroscopy of the knee. Methods and results].
La artroscopia de la rodilla. Metodos y resultados.

L18 ANSWER 67 OF 133 MEDLINE on STN
TI [Cervico-cephalic complications of the automobile accidents. Post-traumatic cervico-cephalic syndrome].
Complicazioni cervico-cefaliche degli incidenti automobilistici. La sindrome cervico-cefalica post-traumatica.

L18 ANSWER 68 OF 133 MEDLINE on STN
TI [Arthroscopy of the knee. Methods and results].
L'artroscopia del ginocchio. Metodi e risultati.

L18 ANSWER 69 OF 133 MEDLINE on STN
TI [Cervicocephalic complications of automobile accidents (cervicocephalic post-traumatic syndrome)].

Complications cervico-cephaliques des accidents d'automobile. (Le syndrome cervico-cephalique post-traumatique.

L18 ANSWER 70 OF 133 MEDLINE on STN
TI [Arthroscopy of the knee (methods and results)].
Arthroscopie du genou (methodes et resultats.

L18 ANSWER 71 OF 133 MEDLINE on STN
TI [Hazards of corticosteroid injections in unrecognized tuberculous arthritis].
I pericoli dell'iniezione di corticosteroidi nelle artriti tubercolari misconosciute.

L18 ANSWER 72 OF 133 MEDLINE on STN
TI [Seronegative rheumatoid polyarthritis. Current status of the question].
Las poliartritis reumatoides seronegativas. Estado actual de la cuestion.

L18 ANSWER 73 OF 133 MEDLINE on STN
TI [Immunosuppressors in rheumatology].
Los inmunodepresores en reumatologia.

L18 ANSWER 74 OF 133 MEDLINE on STN
TI [Degenerated villous tumor of the colon complicated by amyloidosis].
Tumeur villeuse degeneree du colon, compliquee d'amylose.

L18 ANSWER 75 OF 133 MEDLINE on STN
TI [Electromyography of paravertebral muscles; its value in diagnosis of radicular syndromes of the lower extremities].
Electromyographie des muscles para-vertebraux; son interet dans le diagnostic des syndromes radiculaires des membres inferieurs.

L18 ANSWER 76 OF 133 MEDLINE on STN
TI [Senescence and arthrosis].
Senescence et arthrose.

L18 ANSWER 77 OF 133 MEDLINE on STN
TI [Current data on arthritic deterioration of the intervertebral disk].
Donnees actuelles sur la deterioration arthrosique du disque intervertebral.

L18 ANSWER 78 OF 133 MEDLINE on STN
TI [Bouchard's nodes].
La nodosite de Bouchard.

L18 ANSWER 79 OF 133 MEDLINE on STN
TI [Arthroscopy of the knee joint. Current status of the question].
Arthroscopie du genou. Etat actuel de la question.

L18 ANSWER 80 OF 133 MEDLINE on STN
TI [Synovial membrane and synovial fluids. 1967-1968 review].
Synoviale et liquides synoviaux. Bilan 967-1968.

L18 ANSWER 81 OF 133 MEDLINE on STN
TI Electromyography of the paravertebral muscles and its value in the diagnosis of radicular syndromes of the lower limbs.

L18 ANSWER 82 OF 133 MEDLINE on STN
TI [Osseous demineralization and gastrointestinal diseases in adults].
Desmineralizacion osea y afecciones del tubo digestivo del adulto.

L18 ANSWER 83 OF 133 MEDLINE on STN
TI [Dietetics in gout].

Dietetique de la goutte.

L18 ANSWER 84 OF 133 MEDLINE on STN
TI [Electromyography in the tarsal tunnel syndrome].
L'electromyographie du syndrome du tunnel tarsien.

L18 ANSWER 85 OF 133 MEDLINE on STN
TI [The post-traumatic cervico-cephalic syndrome. II. Cephalic syndrome].
Le syndrome cervico-cephalique post-traumatique. II. Le syndrome cephalique.

L18 ANSWER 86 OF 133 MEDLINE on STN
TI [The post-traumatic cervico-- cephalic syndrome. I. Cervical syndrome].
Le syndrome cervico-cephalique post-traumatique. I. Le syndrome cervical.

L18 ANSWER 87 OF 133 MEDLINE on STN
TI [Results of controlled trial of metiazinic acid (16091 RP) in rheumatic pelvi-spondylitis, coxarthrosis and psoriatic rheumatism].
Resultat d'un essai controle de l'acide metiazinique (16091 RP) dans la pelvispondylite rhumatismale, la coxarthrose et le rhumatisme psoriasique.

L18 ANSWER 88 OF 133 MEDLINE on STN
TI [Nystagmographic aspects of vestibular syndromes in cervical post-traumatic syndromes].
Aspects nystagmographiques des syndromes vestibulaires dans les syndromes post-traumatiques cervicaux.

L18 ANSWER 89 OF 133 MEDLINE on STN
TI [Electrology of the carpal tunnel syndrome].
L'electrologie du syndrome du tunnel carpien.

L18 ANSWER 90 OF 133 MEDLINE on STN
TI [The demineralisation of the bony skeleton associated with diseases of the gastro-intestinal tract in adults].
Die Demineralisation des Skelettes bei Erkrankungen des Verdauungstraktes von Erwachsenen.

L18 ANSWER 91 OF 133 MEDLINE on STN
TI [Diet therapy in gout].
Dietetique de la goutte.

L18 ANSWER 92 OF 133 MEDLINE on STN
TI [Osseous demineralization and diseases of the alimentary tract in adults].
Demineralisation osseuse et affections du tube digestif de l'adulte.

L18 ANSWER 93 OF 133 MEDLINE on STN
TI [Seronegative rheumatoid arthritis (current state of the problem)].
Les polyarthrites rhumatoides seronegatives (etat actuel de la question).

L18 ANSWER 94 OF 133 MEDLINE on STN
TI [Immunosuppressive agents in rheumathology].
Les immunodepresseurs en rheumatologie.

L18 ANSWER 95 OF 133 MEDLINE on STN
TI [Semiology of vestibular disorders of cervical origin].
Semiologie des troubles vestibulaires d'origine cervicale.

L18 ANSWER 96 OF 133 MEDLINE on STN
TI [Bone demineralization and diseases of the digestive tract in adults].
Demineralizzazione ossea ed affezioni dell'apparato digerente nell'adulto.

L18 ANSWER 97 OF 133 MEDLINE on STN

TI [Seronegative rheumatoid polyarthritis. Current knowledge of the subject].
Le poliartriti reumatoidi sieronegative. Attuali conoscenze in proposito.

L18 ANSWER 98 OF 133 MEDLINE on STN
TI [The immunosuppressive agents in rheumatology].
Gli immunodepressivi in reumatologia.

L18 ANSWER 99 OF 133 MEDLINE on STN
TI [Osteoarticular manifestations of hemochromatosis].
Les manifestations osteo-articulaires de l'hemochromatose.

L18 ANSWER 100 OF 133 MEDLINE on STN
TI [Immunosuppressive agents in the therapy of rheumatism].
Die Immundepressiva in der Rheumatherapie.

L18 ANSWER 101 OF 133 MEDLINE on STN
TI [Osteoarticular manifestations of hemochromatosis].
Manifestaciones osteoarticulares de la hemocromatosis.

L18 ANSWER 102 OF 133 MEDLINE on STN
TI [Changes of bones and joints in hemochromatosis].
Veranderungen an Knochen und Gelenken bei der Hamochromatose.

L18 ANSWER 103 OF 133 MEDLINE on STN
TI [Current data on the deterioration of the intervertebral disk joint].
Datos actuales sobre la deterioracion artrosica del disco intervertebral.

L18 ANSWER 104 OF 133 MEDLINE on STN
TI [Osteo-articular manifestations of hemochromatosis].
Le manifestazioni osteo-articolari dell'emocromatosi.

L18 ANSWER 105 OF 133 MEDLINE on STN
TI [Electrology of the carpal tunnel syndrome].
L'electrologie du syndrome du tunnel carpien.

L18 ANSWER 106 OF 133 MEDLINE on STN
TI [Hypercalciuria].
Les hypercalciuries.

L18 ANSWER 107 OF 133 MEDLINE on STN
TI Aetiology of the carpal tunnel syndrome.

L18 ANSWER 108 OF 133 MEDLINE on STN
TI [Osseous localizations of mastocytosis].
Les localisations osseuses de la mastocytose.

L18 ANSWER 109 OF 133 MEDLINE on STN
TI [Synovial membrane and synovial fluid in rheumatology. French articles 1967-1968].
Synovialis und Synovia in der Rheumatologie. Franzosische Arbeiten 1967-1968.

L18 ANSWER 110 OF 133 MEDLINE on STN
TI [Synovial membranes and synovial fluid].
Sinoviali e liquido sinoviale.

L18 ANSWER 111 OF 133 MEDLINE on STN
TI [Diffuse osseous mastocytosis. Apropos of a case].
La mastocytose osseuse diffuse. A propos d'un cas.

L18 ANSWER 112 OF 133 MEDLINE on STN
TI [New therapy in female bladder diseases].

Therapeutique nouvelle dans les cystopathies feminines.

L18 ANSWER 113 OF 133 MEDLINE on STN
TI [Treatment of influenzal infections by a moroxydine derivative].
Traitement des affections grippales par un derive de la moroxydine.

L18 ANSWER 114 OF 133 MEDLINE on STN
TI [Methoclopramide in internal medicine and in gastroenterology].
Le metoclopramide en medecine interne et en gastro-enterologie.

L18 ANSWER 115 OF 133 MEDLINE on STN
TI [Our experience with traumatic cervicocephalic syndrome].
Notre experience du syndrome cervicocephalique traumatique.

L18 ANSWER 116 OF 133 MEDLINE on STN
TI [Carpal acroparesthesia. Study of 14 cases of digital acroparesthesia associated with signs of injury of the median nerve at the wrist].
Les acrosyncopes carpiennes. Etude de 14 cas d'acrosyncopes digitales associees a des signes d'atteinte du nerf median au poignet.

L18 ANSWER 117 OF 133 MEDLINE on STN
TI [ACROPARESTHESIA AND CARPAL TUNNEL SYNDROME: A NOSOLOGIC PROBLEM. (APROPOS OF 110 OBSERVATIONS)].
ACROPARESTH'ESIES ET SYNDROME DU CANAL CARPIEN: PROBL'EME NOSOLOGIQUE. (A PROPOS DE 110 OBSERVATIONS).

L18 ANSWER 118 OF 133 MEDLINE on STN
TI [NOCTURNAL ACROPARESTHESIA].
LES ACROPARESTH'ESIES NOCTURNES.

L18 ANSWER 119 OF 133 MEDLINE on STN
TI [POSOLOGY AND RULES OF CLINICAL USE OF METHOCLOPRAMIDE].
POSOLOGIE ET R'EGLES D'EMPLOI CLINIQUE DU M'ETOCLOPRAMIDE.

L18 ANSWER 120 OF 133 MEDLINE on STN
TI Physiopathology of the bladder. Clinical and therapeutic applications.

L18 ANSWER 121 OF 133 MEDLINE on STN
TI On the therapy of hyperthyroidism by perchlorate.

L18 ANSWER 122 OF 133 MEDLINE on STN
TI Endocrine cystalgias.

L18 ANSWER 123 OF 133 MEDLINE on STN
TI Durabolin in bone pathology.

L18 ANSWER 124 OF 133 MEDLINE on STN
TI Spontaneous hemopneumothorax.

L18 ANSWER 125 OF 133 MEDLINE on STN
TI Biermer's anemia following a total gastrectomy.

L18 ANSWER 126 OF 133 MEDLINE on STN
TI Incontinence of effort or orthostatic incontinence in the female.

L18 ANSWER 127 OF 133 MEDLINE on STN
TI [Should one treat certain adenomas of the prostate medically].
Doit-on traiter medicalement certains adenomes prostatiques?.

L18 ANSWER 128 OF 133 MEDLINE on STN
TI [Endocrine cystopathies in women].
Les cystopathies endocrines de la femme.

L18 ANSWER 129 OF 133 MEDLINE on STN
TI [What does urography teach us about the lower urinary tract].
Comment l'urographie renseigne-t-elle sur le bas-appareil urinaire?.

L18 ANSWER 130 OF 133 MEDLINE on STN
TI Le varicocele.

L18 ANSWER 131 OF 133 MEDLINE on STN
TI [Reflections on the treatment of renal tuberculosis; concerning 550 cases observed in 10 years in hospital environment].
Reflexions sur le traitement de la tuberculose renale; a propos de 550 cas observes en 10 ans en milieu hospitalier.

L18 ANSWER 132 OF 133 MEDLINE on STN
TI [Etiological, clinical and therapeutic considerations on pseudocystites in women].
Considerations etiologiques cliniques et therapeutiques sur les fausses cystites de la femme.

L18 ANSWER 133 OF 133 MEDLINE on STN
TI [Bladder diseases of endocrine origin in women].
Essai sur les cystopathies endocrines de la femme.

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L18 ANSWER 14 OF 133 MEDLINE on STN
97442492. PubMed ID: 9295369. Phenotypic alteration of astrocytes induced by ciliary neurotrophic factor in the intact adult brain, As revealed by adenovirus-mediated gene transfer. Lisovoski F; Akli S; Peltekian E; Vigne E; Haase G; Perricaudet M; **Dreyfus P A**; Kahn A; Peschanski M. (Faculte de Medecine, Institut National de la Sante et de la Recherche Medicale Unite 421, Institut Mondor de Medecine Moleculaire, Institut Gustave Roussy, 94010 Creteil Cedex, France.) The Journal of neuroscience : the official journal of the Society for Neuroscience, (1997 Oct 1) Vol. 17, No. 19, pp. 7228-36. Journal code: 8102140. ISSN: 0270-6474. Pub. country: United States. Language: English.
AB Synthesis of the ciliary neurotrophic factor (CNTF) and its specific receptor (CNTFRalpha) is widespread in the intact CNS, but potential biological roles for this system remain elusive. Contradictory results have been obtained concerning a possible effect on the morphological and biochemical phenotype of astrocytes. To reassess this question, we have taken advantage of adenovirus-mediated gene transfer into the rat brain to obtain the local release of CNTF. Stereotaxic administration of CNTF recombinant adenovirus vectors into the striatum led to phenotypic changes in astrocytes located in regions that were related axonally to striatal neurons at the injection site. Astrocytes appeared hypertrophied and displayed an increase in both GFAP and CNTF immunoreactivity. This response was observed up to 5 weeks after injection, the longest time studied. It was not observed after the administration of a control vector. The methodology used in the present study, allowing us to analyze the effect of the factor in areas remote from the injection site, has provided conclusive evidence that CNTF affects the astroglial phenotype in the intact CNS. The characteristics of these effects may explain why contradictory results have been obtained previously, because this signaling system seems to have a low efficiency and therefore requires a high local concentration of the factor close to the target cells. One might speculate as to the involvement of a CNTF astroglio-astroglial signaling system in the organized response of a population of astrocytes to changes in CNS homeostasis detected locally, even by a single cell.

L18 ANSWER 15 OF 133 MEDLINE on STN

97288280. PubMed ID: 9143258. Transforming growth factor alpha expression as a response of murine motor neurons to axonal injury and mutation-induced degeneration. Lisovoski F; Blot S; Lacombe C; Bellier J P; **Dreyfus P A**; Junier M P. (INSERM U421, Fac. Medecine, Creteil, France.) Journal of neuropathology and experimental neurology, (1997 May) Vol. 56, No. 5, pp. 459-71. Journal code: 2985192R. ISSN: 0022-3069. Pub. country: United States. Language: English.

AB We previously showed that degenerating adult motor neurons of the murine mutant wobbler, a model of spinal muscular atrophy, express Transforming Growth Factor alpha (TGF alpha), a growth factor endowed with glio- and neurotrophic activities. Here, we evaluated whether TGF alpha expression is a general response of adult motor neurons to injury. Synthesis of its precursor (pro-TGF alpha) was investigated in another model of motoneuronal degeneration, the murine mutant muscle deficient, and in hypoglossal motor neurons following axonal crush and cut. In control conditions, motor neurons were devoid of pro-TGF alpha immunoreactivity. In the mutant lumbar spinal cord, pro-TGF alpha immunoreactive motor neurons appeared as soon as the disease developed and pro-TGF alpha expression persisted until the latest stages of degeneration. Motor neurons and astrocytes of the white matter weakly immunoreactive for the TGF alpha receptor were also present in both control and mutant lumbar spinal cords. Following hypoglossal nerve crush and cut, motoneuronal pro-TGF alpha expression was precocious and transient, visible at one day post-injury and lasting for only 3 days, during which time astrocyte-like cells immunoreactive for both TGF alpha and its receptor appeared within the injured nucleus. Enhanced TGF alpha mRNA levels following nerve crush showed that activation occurred at the transcriptional level. These results show that upregulation of TGF alpha is an early and common response of adult murine motor neurons to injury, regardless of its experimental or genetic origin.

L18 ANSWER 17 OF 133 MEDLINE on STN

97083333. PubMed ID: 8929907. Targeting widespread sites of damage in dystrophic muscle: engrafted macrophages as potential shuttles. Parrish E P; Cifuentes-Diaz C; Li Z L; Vicart P; Paulin D; **Dreyfus P A**; Peschanski M; Harris A J; Garcia L. (Neuroplasticite et Therapeutique, INSERM U421, Faculte de Medicine, France.) Gene therapy, (1996 Jan) Vol. 3, No. 1, pp. 13-20. Journal code: 9421525. ISSN: 0969-7128. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Inherited muscle diseases are characterized by widespread muscle damage in the body. This limits the clinical relevance of cell or gene therapy based upon direct injections into muscles. One way to circumvent this obstacle would be to use circulating cells, capable of homing naturally to the sites of lesion, to deliver therapeutic substances. Certain muscular dystrophies present successive cycles of degeneration-regeneration. These sporadic necrotic lesions trigger local inflammations with subsequent infiltration of blood-borne mononuclear cells. We have, therefore, tested the possibility that homing monocytes and macrophages could be appropriate shuttles for delivering a therapeutic agent to disseminated pathogenic sites, their targeting being triggered by the pathogeny itself. First, fluorescently labeled immortalized monocytes were intravenously injected into mice which had previously undergone freeze-damaging of individual muscles. In agreement with our hypothesis, intense labelling was observed in the muscle, specifically in damaged regions. Second, the technique was adapted to meet the needs of chronic diseases with characteristic continuous, widespread degeneration of muscle fibers, by creating a reservoir of genetically engineered monocytes, via bone marrow transplantation. Mdx mice received bone marrow from transgenic mice expressing the lacZ reporter gene, under the control of the vimentin promoter, which is active in monocytes and macrophages. Histological and molecular analyses demonstrated the homing of engineered macrophages at

the sites of muscle damage, for periods as long as 2 months. Bone marrow progenitor cells, appropriately engineered to elicit the synthesis, in macrophages, of therapeutically relevant substances, may be of clinical value in various pathologies involving an inflammatory phase.

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E1            2     PARRISH E J/AU
E2            1     PARRISH E N/AU
E3            9 --> PARRISH E P/AU
E4            1     PARRISH ELIZABETH/AU
E5            1     PARRISH ELIZABETH M/AU
E6            3     PARRISH ELOISE/AU
E7            1     PARRISH EVELYN/AU
E8            4     PARRISH F/AU
E9            2     PARRISH F C/AU
E10          20     PARRISH F C JR/AU
E11          13     PARRISH F F/AU
E12           2     PARRISH F J/AU

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L20           9 "PARRISH E P"/AU

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L20  ANSWER 1 OF 9     MEDLINE on STN
97083333.    PubMed ID: 8929907.   Targeting widespread sites of damage in
     dystrophic muscle: engrafted macrophages as potential shuttles. Parrish E
     P; Cifuentes-Diaz C; Li Z L; Vicart P; Paulin D; Dreyfus P A; Peschanski
     M; Harris A J; Garcia L. (Neuroplasticite et Therapeutique, INSERM U421,
     Faculte de Medicine, France. ) Gene therapy, (1996 Jan) Vol. 3, No. 1, pp.
     13-20.  Journal code: 9421525. ISSN: 0969-7128. Pub. country: ENGLAND:
     United Kingdom. Language: English.
AB   Inherited muscle diseases are characterized by widespread muscle damage in
     the body. This limits the clinical relevance of cell or gene therapy
     based upon direct injections into muscles. One way to circumvent this
     obstacle would be to use circulating cells, capable of homing naturally to
     the sites of lesion, to deliver therapeutic substances. Certain muscular
     dystrophies present successive cycles of degeneration-regeneration. These
     sporadic necrotic lesions trigger local inflammations with subsequent
     infiltration of blood-borne mononuclear cells. We have, therefore, tested
     the possibility that homing monocytes and macrophages could be appropriate
     shuttles for delivering a therapeutic agent to disseminated pathogenic
     sites, their targeting being triggered by the pathogeny itself. First,
     fluorescently labeled immortalized monocytes were intravenously injected
     into mice which had previously undergone freeze-damaging of individual
     muscles. In agreement with our hypothesis, intense labelling was observed
     in the muscle, specifically in damaged regions. Second, the technique was
     adapted to meet the needs of chronic diseases with characteristic
     continuous, widespread degeneration of muscle fibers, by creating a
     reservoir of genetically engineered monocytes, via bone marrow
     transplantation. Mdx mice received bone marrow from transgenic mice
     expressing the lacZ reporter gene, under the control of the vimentin
     promoter, which is active in monocytes and macrophages. Histological and
     molecular analyses demonstrated the homing of engineered macrophages at
     the sites of muscle damage, for periods as long as 2 months. Bone marrow
     progenitor cells, appropriately engineered to elicit the synthesis, in
     macrophages, of therapeutically relevant substances, may be of clinical
     value in various pathologies involving an inflammatory phase.

L20  ANSWER 2 OF 9     MEDLINE on STN
92071970.    PubMed ID: 1720465.   Distribution and expression of two
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interactive extracellular matrix proteins, cytotactin and cytotactin-binding proteoglycan, during development of Xenopus laevis. II. Metamorphosis. Williamson D A; **Parrish E P**; Edelman G M. (Rockefeller University, New York, New York 10021.) Journal of morphology, (1991 Aug) Vol. 209, No. 2, pp. 203-13. Journal code: 0406125. ISSN: 0362-2525. Pub. country: United States. Language: English.

AB During metamorphosis of Xenopus laevis the extracellular matrix (ECM) proteins cytotactin and cytotactin-binding (CTB) proteoglycan and the cell adhesion molecules N-CAM and Ng-CAM, appear in highly restricted patterns determined by immunofluorescence histology. During limb development, cytotactin appears from the earliest stages in a meshwork of ECM fibrils associated with migrating mesenchymal cells forming the limb bud. Cytotactin also appears in the ECM between the apical limb ectoderm and mesenchyme. Later, both cytotactin and CTB proteoglycan appear co-localized within the central (prechondrogenic) limb mesenchyme. During chondrogenesis in these areas, cytotactin becomes restricted to perichondrium, while CTB proteoglycan is expressed throughout the cartilage matrix. The premyogenic mesenchyme surrounding the chondrogenic areas expressed N-CAM. Later, N-CAM is concentrated at the myogenic foci where cytotactin appears at sites of nerve/muscle contact and in tendons. Expression of these molecules in the blastemas of regenerating limbs was also studied, and during development of the central nervous system, stomach, and small intestine. Analysis of the expression patterns of cytotactin and CTB proteoglycan throughout development and metamorphosis reveals several consistent themes. The expression of these molecules is highly dynamic, often transient, and associated with key morphogenetic events. Cytotactin appears at multiple sites where cells undergo a transition from an undifferentiated, migratory phenotype to a differentiated phenotype. One or both molecules appear at several sites of border formation between disparate cell collectives, and CTB proteoglycan expression is associated with chondrogenesis.

L20 ANSWER 3 OF 9 MEDLINE on STN

92071969. PubMed ID: 1720464. Distribution and expression of two interactive extracellular matrix proteins, cytotactin and cytotactin-binding proteoglycan, during development of Xenopus laevis. I. Embryonic development. Williamson D A; **Parrish E P**; Edelman G M. (Rockefeller University, New York, New York 10021.) Journal of morphology, (1991 Aug) Vol. 209, No. 2, pp. 189-202. Journal code: 0406125. ISSN: 0362-2525. Pub. country: United States. Language: English.

AB An immunohistochemical study of the localization of cytotactin and cytotactin-binding (CTB) proteoglycan throughout embryonic development of the anuran Xenopus laevis reveals that both appear in a restricted pattern related to specific morphogenetic events. CTB proteoglycan expression is first detected during gastrulation at the blastopore lip. Later, it is seen in the archenteron roof around groups of cells forming the notochord, somites and neural plate. Cytotactin first appears after neurulation, and is restricted to the intersomitic regions. Both molecules appear along the migratory pathways of neural crest cells in the trunk and tail. Later, cytotactin is present at sites where neural crest cells differentiate, around the aorta and in the smooth muscle coat of the gut; CTB proteoglycan is absent from these sites. In the head, cytotactin is initially restricted to the regions between cranial somites, while CTB proteoglycan is distributed throughout the cranial mesenchyme. The expression of both molecules is later associated with key events in chondrogenesis during the development of the skull. After chondrogenesis, CTB proteoglycan is distributed throughout the cartilage matrix, while cytotactin is restricted to a thin perichondrial deposit. Both molecules are expressed in developing brain. These findings are compared to studies of the chick embryo and although distinct anatomical differences exist between frog and chick, the expression of these molecules is associated with similar developmental processes in both species. These include

mesoderm segmentation, neural crest cell migration and differentiation, cartilage development, and central nervous system histogenesis.

L20 ANSWER 4 OF 9 MEDLINE on STN

91009551. PubMed ID: 2120245. Size heterogeneity, phosphorylation and transmembrane organisation of desmosomal glycoproteins 2 and 3 (desmocollins) in MDCK cells. **Parrish E P**; Marston J E; Mattey D L; Measures H R; Venning R; Garrod D R. (Cancer Research Campaign Medical Oncology Unit, University of Southampton, UK.) Journal of cell science, (1990 Jun) Vol. 96 (Pt 2), pp. 239-48. Journal code: 0052457. ISSN: 0021-9533. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Metabolic labelling with [35S]methionine and immunoprecipitation with specific antibodies to bovine desmosomal glycoproteins 2 and 3 (dg2 and dg3: desmocollins) reveals a triplet of polypeptides of Mr 115,000, 107,000 and 104,000 in MDCK cells. Tunicamycin treatment shows that this heterogeneity does not arise through differential N-linked glycosylation. Under conditions in which cells are actively forming desmosomes, the largest polypeptide, dg2, becomes phosphorylated on serine, but the two smaller polypeptides, dg3a and 3b, do not. Controlled trypsinisation of intact cells yields three membrane-protected fragments (Mr 28,000, 24,000 and 23,000) derived from these glycoproteins. The largest of these fragments is phosphorylated but the two smaller fragments are not. A monoclonal antibody to bovine dg2 and dg3 stains MDCK cells cytoplasmically. In immunoblotting of MDCK cells the monoclonal antibody recognises dg2 strongly and shows a weaker reaction with a band of lower Mr corresponding to dg3a. It also recognises the immunoprecipitated 28,000 Mr fragment from trypsinised cells and a smaller fragment of 24,000 Mr. The simplest interpretation of these data is that all three glycoproteins have a transmembrane configuration with a single membrane-spanning domain, and show heterogeneity of size and phosphorylation in their cytoplasmic domains. The data are discussed in relation to the known structures of some cell adhesion molecules. Questions about the relative roles and distributions of the different polypeptides in desmosomal organisation are raised.

L20 ANSWER 5 OF 9 MEDLINE on STN

88233157. PubMed ID: 3374751. The cranial arachnoid and pia mater in man: anatomical and ultrastructural observations. Alcolado R; Weller R O; **Parrish E P**; Garrod D. (Neuropathology and Medical Oncology, Southampton University Medical School, UK.) Neuropathology and applied neurobiology, (1988 Jan-Feb) Vol. 14, No. 1, pp. 1-17. Journal code: 7609829. ISSN: 0305-1846. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The objects of the present study were: (1) to define the relationships of the arachnoid mater to blood vessels in the subarachnoid space; (2) to establish the structure of leptomeningeal trabeculae and their relationships to the pia mater; and (3) to investigate the fine structure of the human pia mater. Intracranial portions of vertebral artery were taken at post mortem, and normal cerebral cortex and overlying leptomeninges were obtained from surgical lobectomies. Tissue from these specimens was examined by scanning and transmission electron microscopy, by light microscopy and by immunocytochemistry for the presence of basement membrane, desmosomal proteins and vimentin. Results of the study showed that as the vertebral artery pierced the posterior atlanto-occipital membrane and entered the subarachnoid space, it acquired a leptomeningeal coat as the arachnoid was reflected on to it. It has been demonstrated previously that as vessels enter the brain, the leptomeningeal coat is reflected on to the surface of the cortex as the pia mater. The arachnoid mater was seen to consist of a subdural mesothelial layer and a compact central layer as previously reported. From the inner layer of the arachnoid, collagen bundles coated by leptomeningeal cells extended as trabeculae across the subarachnoid space to fuse with the pia mater. The pia itself was composed of a delicate but

apparently continuous layer of cells joined by desmosomes and gap junctions but no tight junctions were observed. It was possible to detect pia mater cells in the perivascular spaces of the brain by immunocytochemical techniques using light microscopy. The significance of the observed anatomical arrangement for cerebrospinal fluid physiology is discussed.

L20 ANSWER 6 OF 9 MEDLINE on STN

88117978. PubMed ID: 3323436. Monoclonal antibody to desmosomal glycoprotein 1--a new epithelial marker for diagnostic pathology. Vilela M J; **Parrish E P**; Wright D H; Garrod D R. (Cancer Research Campaign Medical Oncology Unit, University of Southampton, Southampton General Hospital, U.K.) The Journal of pathology, (1987 Dec) Vol. 153, No. 4, pp. 365-75. Journal code: 0204634. ISSN: 0022-3417. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Desmosomes are intercellular adhesive junctions that occur in almost all epithelia and should therefore be useful as epithelial markers in tumour diagnosis. Here, we describe a monoclonal antibody, 32-2B, to a major desmosomal glycoprotein (dgl) which reacts with human tissues in paraffin sections. This antibody was tested for its ability to stain epithelia and tumours. It reacted with all epithelia tested and with every specimen of a wide range of carcinomas. It also stained meningiomas, another desmosome-containing tumour. It did not stain other types of tumours including lymphomas, melanomas, and various sarcomas, or normal tissues which lack desmosomes. These characteristics demonstrate that 32-2B is a reliable epithelial marker that may have a useful role in diagnostic histopathology.

L20 ANSWER 7 OF 9 MEDLINE on STN

88117966. PubMed ID: 3323433. Antidesmosomal monoclonal antibody in the diagnosis of intracranial tumours. **Parrish E P**; Steart P V; Garrod D R; Weller R O. (Cancer Research Campaign Medical Oncology Unit, Southampton General Hospital, U.K.) The Journal of pathology, (1987 Nov) Vol. 153, No. 3, pp. 265-73. Journal code: 0204634. ISSN: 0022-3417. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Immunocytochemistry has been applied extensively to the diagnosis of intracranial tumours, but meningiomas still present a diagnostic problem. However, desmosomes have been shown by electron microscopy to be present in meningiomas, and this distinguishes them from gliomas. This paper describes a new monoclonal antibody, 11-5F, against desmosomal proteins 1 and 2 (desmoplakins) and assesses its usefulness in the diagnosis of meningiomas and other intracranial tumours. A total of 74 surgically removed intracranial tumours were examined by fluorescent antibody staining with 11-5F on frozen sections. In addition, a panel of antibodies against cytokeratin, vimentin, glial fibrillary acidic protein, and S100 protein was used. 11-5F stained 30/30 meningiomas and 14/14 metastatic carcinomas but 0/30 gliomas, thus distinguishing meningiomas and metastatic carcinomas from gliomas. The distinction between meningiomas and metastatic carcinomas on the basis of intermediate filaments staining was more difficult because neither the anticytokeratin nor the antivimentin antibody was specific for either tumour type. This study emphasizes the value of antidesmosomal antibodies as an important adjunct to the diagnosis of intracranial tumours.

L20 ANSWER 8 OF 9 MEDLINE on STN

88083941. PubMed ID: 3691948. The structure of desmosomes and their role in malignant disease. Garrod D R; **Parrish E P**; Marston J E. (C.R.C. Medical Oncology Unit, Southampton General Hospital, U.K.) Biochemical Society transactions, (1987 Oct) Vol. 15, No. 5, pp. 802-4. Journal code: 7506897. ISSN: 0300-5127. Pub. country: ENGLAND: United Kingdom. Language: English.

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L20  ANSWER 9 OF 9      MEDLINE on STN
86206011.     PubMed ID: 3517874.   Mouse antisera specific for desmosomal
      adhesion molecules of suprabasal skin cells, meninges, and meningioma.
      Parrish E P; Garrod D R; Mattey D L; Hand L; Steart P V; Weller R O.
      Proceedings of the National Academy of Sciences of the United States of
      America, (1986 Apr) Vol. 83, No. 8, pp. 2657-61.  Journal code: 7505876.
      ISSN: 0027-8424. Pub. country: United States. Language: English.
AB    Mouse polyclonal antisera were raised to the Mr 130,000 and Mr 115,000
      cell surface glycoproteins, desmocollins, of desmosomes from bovine nasal
      epithelium. Immunoblotting confirmed that the antisera were specific for
      the desmocollins. An immunofluorescence study showed that the antisera
      distinguished between the basal and suprabasal layers of bovine and human
      epidermis. The antibodies reacted with cultured keratinocytes only after
      calcium-induced stratification. In epidermis, therefore, there appears to
      be a difference between the desmocollins of basal and suprabasal cells
      that may be important in relation to epidermal differentiation. Previous
      work has shown that polyclonal antisera raised in other animals (guinea
      pigs and rabbits) against desmocollins, as well as against other
      desmosomal components, react with all desmosome-containing epithelia. In
      contrast, an immunofluorescence survey of bovine, rat, and human tissues
      showed that the present mouse antisera stained only suprabasal skin cells
      and the arachnoid layer of the meninges, demonstrating that these have
      common determinants that distinguished their desmocollins from those of
      all other tissues. The antibodies also stained 11 of 12 meningiomas and,
      therefore, may be useful as a marker not only for the diagnosis of these
      tumors but also for investigation of their histogenesis.


=> e peltekian e/au
E1            1     PELTEKIAN C/AU
E2            1     PELTEKIAN CECILE/AU
E3            5 --> PELTEKIAN E/AU
E4            2     PELTEKIAN ELISE/AU
E5            9     PELTEKIAN K/AU
E6            8     PELTEKIAN K M/AU
E7            6     PELTEKIAN KEVORK/AU
E8            9     PELTEKIAN KEVORK M/AU
E9            6     PELTEKOVA V/AU
E10           6     PELTEKOVA V D/AU
E11           1     PELTEKOVA V T/AU
E12           3     PELTEKOVA VANYA/AU

=> s e3-e4
              5 "PELTEKIAN E"/AU
              2 "PELTEKIAN ELISE"/AU
L21           7 ("PELTEKIAN E"/AU OR "PELTEKIAN ELISE"/AU)

=> d his

     (FILE 'HOME' ENTERED AT 16:51:29 ON 28 SEP 2006)

     FILE 'USPATFULL' ENTERED AT 16:51:54 ON 28 SEP 2006
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L1            2 S E4
                E PARRISH ELAINE/IN
L2            2 S E3
L3            0 S L2 NOT L1
                E GARCIA LUIS/IN
L4           27 S E3-E5
L5           25 S L4 NOT L1
L6            0 S L5 AND (MONOCYT? OR MACROPHAG? OR PHAGOCYT?)
                E PELTEKIAN ELISE/IN
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L7             3 S E3
L8             1 S L7 NOT L1
                 E BARTHOLEYNS JACQUE/IN
L9            23 S E4
L10           21 S L9 NOT L1

     FILE 'WPIDS' ENTERED AT 16:59:22 ON 28 SEP 2006
                 E DREYFUS P A/IN
L11            1 S E3
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L12            1 S E3
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L14           40 S E3
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L16            2 S E3
L17            1 S L16 NOT L11

     FILE 'MEDLINE' ENTERED AT 17:02:36 ON 28 SEP 2006
                 E DREYFUS P A/AU
L18          133 S E2 OR E3
L19            3 S L18 AND (MONOCYT? OR MACROPHAG? OR PHAGOCYT?)
                 E PARRISH E P/AU
L20            9 S E3
                 E PELTEKIAN E/AU
L21            7 S E3-E4

=> s l21 not (l18 or l20)
L22            6 L21 NOT (L18 OR L20)

=> d l22,ti,1-6

L22  ANSWER 1 OF 6      MEDLINE on STN
TI   Different expression of synemin isoforms in glia and neurons during
     nervous system development.

L22  ANSWER 2 OF 6      MEDLINE on STN
TI   FGF6 mediated expansion of a resident subset of cells with SP phenotype in
     the C2C12 myogenic line.

L22  ANSWER 3 OF 6      MEDLINE on STN
TI   Neurotropism and retrograde axonal transport of a canine adenoviral
     vector: a tool for targeting key structures undergoing neurodegenerative
     processes.

L22  ANSWER 4 OF 6      MEDLINE on STN
TI   Computerised dystrophic muscle simulator: prospecting potential
     therapeutic strategies for muscle dystrophies using a virtual experimental
     model.

L22  ANSWER 5 OF 6      MEDLINE on STN
TI   Blood borne macrophages are essential for the triggering of muscle
     regeneration following muscle transplant.

L22  ANSWER 6 OF 6      MEDLINE on STN
TI   Adenovirus-mediated gene transfer to the brain: methodological assessment.


=> d l22,cbib,ab,5,6

L22  ANSWER 5 OF 6      MEDLINE on STN
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1999237210. PubMed ID: 10220861. Blood borne macrophages are essential for the triggering of muscle regeneration following muscle transplant. Lescaudron L; **Peltekian E**; Fontaine-Perus J; Paulin D; Zampieri M; Garcia L; Parrish E. (CNRS EP 1593, Faculte des Sciences et des Techniques, Nantes, France.. lescaud@nat.svt.sciences.univ-nantes.fr) . Neuromuscular disorders : NMD, (1999 Mar) Vol. 9, No. 2, pp. 72-80. Journal code: 9111470. ISSN: 0960-8966. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The transplantation of satellite cells may constitute a strategy for rebuilding muscle fibres in inherited myopathies. However, its development requires a great understanding of the role of environmental signals in the regenerative process. It is therefore essential to identify the key events triggering and controlling this process in vivo. We investigated whether macrophages play a key role in the course of the regenerative process using skeletal muscle transplants from transgenic pHuDes-nls-LacZ mice. Before grafting, transplants were conditioned with macrophage inflammatory protein 1-beta (MIP 1-beta; stimulating the macrophages infiltration or vascular endothelial growth factor (VEGF) stimulating angiogenesis). Treatment of transplants with MIP 1-beta and VEGF both accelerated and augmented monocyte-macrophage infiltration and satellite cell differentiation and/or proliferation, as compared to controls. In addition, VEGF treatment enhanced the number of newly formed myotubes. When a complete depletion of host monocyte-macrophages was experimentally induced, no regeneration occurred in transplants. Our data suggest that the presence of blood borne macrophages is required for triggering the earliest events of skeletal muscle regeneration. The understanding of macrophage behaviour after muscle injury should allow us to develop future strategies of satellite cell transplantation as a treatment for muscular dystrophies.

L22 ANSWER 6 OF 6 MEDLINE on STN

97270294. PubMed ID: 9125377. Adenovirus-mediated gene transfer to the brain: methodological assessment. **Peltekian E**; Parrish E; Bouchard C; Peschanski M; Lisovoski F. (INSERM Unit 421, Faculte de Medecine, Creteil, France.) Journal of neuroscience methods, (1997 Jan) Vol. 71, No. 1, pp. 77-84. Ref: 37. Journal code: 7905558. ISSN: 0165-0270. Pub. country: Netherlands. Language: English.

AB The purpose of this short review is to analyse major advantages and limitations of the adenovirus (Ad), specifically with relevance to its use as a vector for gene transfer to the brain. The characteristics of Ad transduction include: the relative absence of cell type specificity; the limited spatial spread of the virus; and the long-term expression of the transgene. In the central nervous system, in contrast to that which occurs in other organs, Ad transduction in the adult does not systematically provoke cell death. Nevertheless, a proportion of the transduced cells do die, and this represents a conspicuous problem. Mechanisms leading to cell death in the brain may include immune rejection and inflammation-related toxicity, although this would not explain all of the results, and direct toxicity related to either inappropriate preparation or the transduction itself. Taking into account uncertainties concerning the innocuousness of Ad transduction, it may seem unwise to envisage Ad gene therapy for diseases that are not life-threatening and/or benefit from adequate drug or surgical treatments (e.g. Parkinson's disease or epilepsy). Ad vectors may not be easily used either in diseases displaying major immune dysfunction (e.g. multiple sclerosis). In contrast, malignant brain tumors and numerous neurodegenerative diseases (such as Huntington's, Alzheimer's diseases or amyotrophic lateral sclerosis) are directly life-threatening and deprived of any adequate treatment. They may be appropriate targets for Ad-mediated gene therapy, once both the vector and the gene of interest have been defined and optimized.

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L3            0 S L2 NOT L1
                E GARCIA LUIS/IN
L4           27 S E3-E5
L5           25 S L4 NOT L1
L6            0 S L5 AND (MONOCYT? OR MACROPHAG? OR PHAGOCYT?)
                E PELTEKIAN ELISE/IN
L7            3 S E3
L8            1 S L7 NOT L1
                E BARTHOLEYNS JACQUE/IN
L9           23 S E4
L10          21 S L9 NOT L1

     FILE 'WPIDS' ENTERED AT 16:59:22 ON 28 SEP 2006
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L13           0 S L12 NOT L11
                E GARCIA L/IN
L14          40 S E3
L15           1 S L14 AND (MONOCYT? OR MACROPHAGE OR PHAGOCYT?)
                E PELTEKIAN E/IN
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L17           1 S L16 NOT L11

     FILE 'MEDLINE' ENTERED AT 17:02:36 ON 28 SEP 2006
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L18         133 S E2 OR E3
L19           3 S L18 AND (MONOCYT? OR MACROPHAG? OR PHAGOCYT?)
                E PARRISH E P/AU
L20           9 S E3
                E PELTEKIAN E/AU
L21           7 S E3-E4
L22           6 S L21 NOT (L18 OR L20)

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COST IN U.S. DOLLARS                        SINCE FILE      TOTAL
                                               ENTRY    SESSION
FULL ESTIMATED COST                            11.83     111.13

FILE 'USPATFULL' ENTERED AT 17:15:32 ON 28 SEP 2006
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FILE LAST UPDATED: 28 Sep 2006 (20060928/ED)
HIGHEST GRANTED PATENT NUMBER: US7114185
HIGHEST APPLICATION PUBLICATION NUMBER: US2006218687
CA INDEXING IS CURRENT THROUGH 28 Sep 2006 (20060928/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 28 Sep 2006 (20060928/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Jun 2006
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Jun 2006
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=> s (monocyte or macrophage or phagocyte)
         14087 MONOCYTE
         26608 MACROPHAGE
          1780 PHAGOCYTE
L23      32398 (MONOCYTE OR MACROPHAGE OR PHAGOCYTE)

=> s l23 and (monocyte?/clm or macrophag?/clm or phagocyt?/clm)
          1587 MONOCYTE?/CLM
          2828 MACROPHAG?/CLM
           460 PHAGOCYT?/CLM
L24       3479 L23 AND (MONOCYTE?/CLM OR MACROPHAG?/CLM OR PHAGOCYT?/CLM)

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          6520 CARGO/CLM
         62328 LOADED/CLM
L25         59 L24 AND (CARGO/CLM OR LOADED/CLM)

=> d his

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                E GARCIA LUIS/IN
L4           27 S E3-E5
L5           25 S L4 NOT L1
L6            0 S L5 AND (MONOCYT? OR MACROPHAG? OR PHAGOCYT?)
                E PELTEKIAN ELISE/IN
L7            3 S E3
L8            1 S L7 NOT L1
                E BARTHOLEYNS JACQUE/IN
L9           23 S E4
L10          21 S L9 NOT L1

     FILE 'WPIDS' ENTERED AT 16:59:22 ON 28 SEP 2006
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                E GARCIA L/IN
L14          40 S E3
L15           1 S L14 AND (MONOCYT? OR MACROPHAGE OR PHAGOCYT?)
                E PELTEKIAN E/IN
L16           2 S E3
L17           1 S L16 NOT L11

     FILE 'MEDLINE' ENTERED AT 17:02:36 ON 28 SEP 2006
                E DREYFUS P A/AU
L18         133 S E2 OR E3
L19           3 S L18 AND (MONOCYT? OR MACROPHAG? OR PHAGOCYT?)
                E PARRISH E P/AU
L20           9 S E3
                E PELTEKIAN E/AU
L21           7 S E3-E4
L22           6 S L21 NOT (L18 OR L20)
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L25           59 S L24 AND (CARGO/CLM OR LOADED/CLM)

=> s l25 not (l1 or l4 or l9 or l7)
L26           54 L25 NOT (L1 OR L4 OR L9 OR L7)

=> d l26,cbib,clm,1-54

L26  ANSWER 1 OF 54  USPATFULL on STN
2006:236026 Methods for treating cancers and pathogen infections using
    antigen-presenting cells loaded with RNA.
    Nair, Smita K., Durham, NC, UNITED STATES
    Boczkowski, David J., Durham, NC, UNITED STATES
    Gilboa, Eli, Durham, NC, UNITED STATES
    Duke University, Durham, NC, UNITED STATES (U.S. corporation)
    US 7105157 B1 20060912
    WO 9741210  19971106
    APPLICATION: US 1997-171916  19970430 (9)
    WO 1997-US7317 19970430 19990216  PCT 371 date
    DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM    What is claimed is:
       1. A method for producing an RNA-loaded antigen presenting cell (APC)
       that presents on its surface a tumor antigenic epitope encoded by RNA of
       a tumor, wherein the epitope induces T cell proliferation, said method
       comprising: introducing into an antigen-presenting cell in vitro RNA of
       a tumor comprising tumor-specific RNA that encodes an antigen that
       induces T cell proliferation and tumor immunity, thereby producing an
       RNA-loaded APC that presents on its surface a tumor antigenic epitope
       encoded by the RNA of the tumor, wherein the epitope induces T cell
       proliferation.

       2. The method of claim 1, wherein said APC is a dendritic cell.

       3. The method of claim 1, wherein said APC is a macrophage.

       4. The method of claim 1, wherein said APC is an endothelial cell.

       5. The method of claim 1, wherein said APC is an artificially generated
       APC.

       6. The method of claim 1, wherein said RNA comprises poly A+ RNA.

       7. The method of claim 1, wherein said RNA comprises cytoplasmic RNA.

       8. The method of claim 1, wherein the RNA is introduced into the APC by
       contacting the APC with the RNA in the presence of a cationic lipid.

       9. The method of claim 1, wherein said RNA is provided as a fiactionated
       tumor extract that is fiactionated with respect to a non-RNA component
       of the tumor extract.

       10. The method of claim 1, further comprising introducing into the APC
       RNA encoding an immunomodulator.

       11. An isolated RNA-loaded APC produced by the method of claim 1.

       12. The method of claim 1, wherein the RNA is obtained from fixed
       tissue.
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13. The method of claim 1, wherein the RNA is obtained from a melanoma.

14. The method of claim 1, wherein the RNA is obtained from a bladder tumor.

15. The method of claim 1, wherein the RNA is obtained from a tumor selected from the group consisting of a breast cancer tumor, a colon cancer tumor, a prostate cancer tumor, and an ovarian cancer tumor.

16. The method of claim 1, wherein said RNA is prepared by amplification and in vitro transcription.

17. The method of claim 1, wherein said RNA comprises nuclear RNA.

18. The method of claim 1 wherein said RNA comprises a minigene.

19. The method of claim 1, wherein said RNA is prepared by in vitro transcription.

20. The method of claim 1, wherein said RNA comprises a sequence that encodes a polypeptide which controls intracellular trafficking of a polypeptide to which it is attached.

21. The method of claim 10, wherein the immunomodulator is a cytokine.

22. The method of claim 10, wherein the immunomodulator is a costimulatory factor.

23. A method for treating a tumor in a patient, said method comprising administering to the patient a therapeutically effective amount of the RNA-**loaded** APC of claim 11.

24. A method for producing a cytotoxic T lymphocyte that is cytotoxic for a cell which presents a tumor antigen (CTL), said method comprising: providing a T lymphocyte; contacting said T lymphocyte in vitro with the RNA-**loaded** APC of claim 11; and maintaining said T lymphocyte under conditions conducive to CTL proliferation, thereby producing a CTL that is cytotoxic for a cell which presents a tumor antigen.

25. A method for treating a tumor in a patient, said method comprising: i) producing a cytotoxic T lymphocyte that is cytotoxic for a cell that presents a tumor antigen, said cytotoxic T lymphyocyte being produced by a method comprising the steps of: a) providing a T lymphocyte; b) contacting said T lymphocyte in vitro with the RNA-**loaded** antigen presenting cell of claim 11; and c) maintaining said T lymphocyte under conditions conducive to cytotoxic T lymphocyte proliferation, thereby producing said cytotoxic T lymphocyte that is cytotoxic for said cell that presents said tumor antigen, and ii) administering to said patient a therapeutically effective amount of said cytotoxic T lymphocyte.

26. The method of claim 23, wherein the RNA is obtained from said patient.

27. The method of claim 23, wherein the RNA is obtained from a donor patient.

28. The method of claim 24, wherein the RNA comprises at least 80% of polyA+ RNA naturally present in a tumor cell.

29. A method for producing an RNA-**loaded** antigen presenting cell (APC) that presents on its surface a pathogen antigenic epitope encoded by the RNA, wherein the epitope induces T cell proliferation, said method

comprising: introducing into an antigen-presenting cell in vitro RNA of a pathogen consisting essentially of RNA encoding a pathogen antigen that induces T cell proliferation and an immune response to the pathogen, thereby producing an RNA-**loaded** APC that presents on its surface a pathogen antigenic epitope encoded by the RNA, wherein the epitope induces T cell proliferation.

30. The method of claim 29, wherein said APC is selected from the group consisting of dendritic cells, **macrophages**, and endothelial cells.

31. The method of claim 29, wherein said APC is an artificially generated APC.

32. The method of claim 29, wherein said RNA comprises poly A+ RNA.

33. The method of claim 29, wherein said RNA is obtained from a virus.

34. The method of claim 29, wherein said RNA is obtained from a bacterium.

35. A method for producing a cytotoxic T lymphocyte (CTL) that is cytotoxic for a cell which presents a pathogen antigen, said method comprising: providing a T lymphocyte; contacting said T lymphocyte in vitro with the RNA-**loaded** APC produced by the method of claim 29; and maintaining said T lymphocyte under conditions conducive to CTL proliferation, thereby producing a CTL that is cytotoxic for a cell which presents a pathogen antigen.

36. The method of claim 29, wherein said RNA comprises a sequence that encodes a trafficking sequence.

37. A method for treating a pathogen infection in a patient, said method comprising: i) producing a cytotoxic T lymphocyte that is cytotoxic for a cell that presents an antigen of said pathogen, said cytotoxic T lymphyocyte being produced by a method comprising the steps of a) providing a T lymphocyte; b) contacting said T lymphocyte in vitro with the RNA-**loaded** antigen presenting cell produced by the method of claim 29; and c) maintaining said T lymphocyte under conditions conducive to cytotoxic T lymphocyte proliferation, thereby producing said cytotoxic T lymphocyte that is cytotoxic for a cell that presents said antigen of said pathogen, and ii) administering to said patient a therapeutically effective amount of said cytotoxic T lymphocyte.

38. The method of claim 37, wherein said virus is selected from the group consisting of Hepatitis viruses, human immunodeficiency viruses, influenza viruses, poliomyelitis viruses, measles viruses, herpes viruses, mumps viruses, and rubella viruses.

39. The method of claim 34, wherein said bacterium is selected from the group consisting of Salmonella, Shigella, and Enterobacter.

40. The method of claim 28, further comprising detecting sensitization of the contacted T lymphocyte as an indication of the induction of a CTL response.

41. The method of claim 40, wherein sensitization is detected in a cytotoxicity assay that comprises detecting killing of an RNA-**loaded** cell that presents on its surface a tumor or pathogen antigenic epitope encoded by RNA.

42. The method of claim 40, wherein sensitization of the contacted T lymphocyte is detected as an increase in cytokine secretion by the T

lymphocyte.

43. The method of claim 20, wherein said polypeptide that controls intracellular trafficking is KDEL (SEQ ID NO: 1); KFERQ (SEQ ID NO: 2); QREK (SEQ ID NO: 3); MAISGVPVLGFFIIAVLMSAQESWA (SEQ ID NO: 4); a pentapeptide comprising Q flanked on one side by four residues selected from the group consisting of K, R, D, E, F, I, V, and L; or a signal peptide.

44. A method for detecting an increase in tumor-specific or pathogen-specific CTL in a patient, the method comprising: i) contacting a first sample of T lymphocyte from the patient in vitro with RNA-**loaded** APCs that present a cell-surface tumor or pathogen antigenic epitope encoded by the RNA, thereby producing a first expanded sample of T lymphocytes; ii) administering to the patient the RNA-**loaded** APCs that present a cell-surface tumor or pathogen antigenic epitope encoded by RNA; iii) subsequent to the administering step, contacting a second sample of T lymphocytes from the patient in vitro with RNA-**loaded** APCs that present a cell-surface tumor or pathogen antigenic epitope encoded by the RNA, thereby producing a second expanded sample of T lymphocytes; iv) comparing sensitization of the first expanded sample of T lymphocytes with sensitization of the second expanded sample of T lymphocytes, wherein an increased level of sensitization in the second sample, as compared with the first sample, is an indicator of an increase in tumor-specific or pathogen-specific CTL.

45. The method of claim 44, wherein sensitization is measured in a cytotoxicity assay.

46. The method of claim 25, wherein the T lymphocyte is obtained from said patient.

47. The method of claim 25, wherein the T lymphocyte is obtained from a donor patient.

48. The method of claim 25, wherein the RNA is obtained from a tumor of said patient.

49. The method of claim 25, wherein the RNA is obtained from a donor patient.

L26 ANSWER 2 OF 54 USPATFULL on STN
2006:202127 Medical treatment.
Champion, Brian Robert, Cambridge, UNITED KINGDOM
Ragno, Silvia, Cambridge, UNITED KINGDOM
US 2006172011 A1 20060803
APPLICATION: US 2005-232404 A1 20050921 (11)
PRIORITY: GB 2003-6583 20030321
GB 2003-6582 20030321
GB 2003-6621 20030322
GB 2003-6622 20030322
GB 2003-6626 20030322
GB 2003-6624 20030322
GB 2003-6640 20030322
GB 2003-6644 20030322
GB 2003-6650 20030322
GB 2003-6651 20030322
GB 2003-6654 20030322
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

CLM What is claimed is:

1. A particle capable of being inserted into or taken up by a cell comprising: i) a polynucleotide coding for a modulator of Notch signalling; ii) a polynucleotide coding for an antigen or antigenic determinant thereof; and iii) optionally, a matrix, carrier or substrate wherein one or both polynucleotides are borne within or on the surface of the matrix, carrier or substrate.

2. The particle as claimed in claim 1 in the form of a microparticle.

3. (canceled)

4. The particle as claimed in claim 1, wherein the cell is an immune cell.

5. The particle as claimed in claim 4, wherein the immune cell is an antigen presenting cell.

6. (canceled)

7. (canceled)

8. The particle as claimed in claim 1, which is capable of being inserted into a cell by a ballistic/biolistic delivery method.

9. (canceled)

10. The particle as claimed in claim 1, which is capable of being taken up by a cell by endocytosis or **phagocytosis**.

11. (canceled)

12. (canceled)

13. The particle as claimed in claim 1, wherein the polynucleotide coding for a modulator of Notch signalling codes for an activator of Notch signalling.

14. The particle as claimed in claim 1, wherein the polynucleotide coding for a modulator of Notch signalling codes for an inhibitor of Notch signalling.

15. (canceled)

16. (canceled)

17. The particle as claimed in claim 1, wherein the polynucleotide coding for the modulator of Notch signalling codes for: (i) a polypeptide comprising a Notch ligand or an active fragment, derivative, homologue, analogue or allelic variant thereof; (ii) a fusion protein comprising a segment of a Notch ligand extracellular domain and an immunoglobulin Fc segment: (iii) a protein or polypeptide comprising a Notch ligand DSL domain, at least one EGF-like domain, and optionally a membrane-binding or transmembrane domain; (iv) Notch intracellular domain (Notch IC) or a fragment, derivative, homologue, analogue or allelic variant thereof; or (v) a dominant negative version of a Notch signalling repressor.

18. The particle as claimed in claim 17, wherein the Notch ligand is Delta or Serrate/Jagged protein or a fragment, derivative, homologue, analogue or allelic variant thereof.

19-25. (canceled)

26. The particle as claimed in claim 1, wherein the polynucleotide coding for the modulator of Notch signalling codes for a polypeptide capable of upregulating the expression or activity of a Notch ligand or a downstream component of the Notch signalling pathway.

27. The particle as claimed in claim 1, wherein the antigen or antigenic determinant is: (i) an allergen or antigenic determinant thereof; (ii) an autoantigen or antigenic determinant thereof; (iii) an MHC or transplant antigen or antigenic determinant thereof; (iv) a pathogen antigen or antigenic determinant thereof; or (v) a tumour antigen or antigenic determinant thereof.

28-31. (canceled)

32. The particle as claimed in claim 1 comprising a liposomal structure.

33. The particle as claimed in claim 1, which is suitable for transdermal, intradermal, or mucosal delivery to a subject or administration to a subject by means of a needleless syringe or biolistic delivery device.

34. (canceled)

35. The particle as claimed in claim 1 having a size of from about 0.005 to about 500 micrometres.

36. (canceled)

37. (canceled)

38. The particle as claimed in claim 1 comprising a carrier particle.

39. The particle as claimed in claim 38, wherein the carrier particle is a metal particle.

40. The particle as claimed in claim 39, wherein the carrier particle is selected from tungsten, gold, platinum and iridium particles.

41. (canceled)

42. The particle as claimed in claim 1 comprising a polymeric matrix or carrier or a lipid matrix or carrier.

43. (canceled)

44. The particle as claimed in claim 42, wherein the lipid is selected from the group consisting of a cationic lipid, an anionic lipid, and a zwitterionic lipid.

45. The particle as claimed in claim 42, wherein the lipid comprises cetyltrimethylammonium.

46. The particle as claimed in claim 42, wherein the lipid comprises a phospholipid.

47. (canceled)

48. The particle as claimed in claim 1, wherein one or both of the polynucleotides comprises an expression control sequence operatively linked to a coding sequence.

49. The particle as claimed in claim 48, wherein one or both of the polynucleotides is present in an expression vector.

50. (canceled)

51. (canceled)

52. The particle as claimed in claim 1 further comprising a targeting molecule.

53. The particle as claimed in claim 1 further comprising a stabilizer.

54. The particle as claimed in claim 1, wherein one or both of the polynucleotides codes for a trafficking sequence selected from the group consisting of a sequence which trafficks to endoplasmic reticulum, a sequence which trafficks to a lysosome, a sequence which trafficks to an endosome, a sequence which trafficks to an intracellular vesicle, and a sequence which trafficks to the nucleus.

55-59. (canceled)

60. The A particle as claimed in claim 1, wherein at least about 10% of the polynucleotide, by weight, comprises supercoiled DNA molecules.

61. (canceled)

62. (canceled)

63. A composition comprising the particle as claimed in claim 1.

64. A method for preparing the particle as claimed in claim 1 comprising combining (in any order): i) a polynucleotide coding for a modulator of Notch signalling; ii) a polynucleotide coding for an antigen or antigenic determinant thereof; and optionally a substrate, matrix or carrier.

65. A method for modulating an immune response to an antigen in a subject by administering the particle as claimed in claim 1 to a subject in need thereof.

66. (canceled)

67. (canceled)

68. A method for modifying an immune response to an antigen or antigenic determinant in a subject by causing to be inserted into or taken up by a cell in the subject: i) a polynucleotide coding for a modulator of Notch signalling; and ii) a polynucleotide coding for the antigen or antigenic determinant thereof; whereby expression of the polynucleotides in the cell modifies an immune response to the antigen or antigenic determinant in the subject.

69. The method as claimed in claim 68, wherein the antigen or antigenic determinant is an allergen, autoantigen, tumour antigen or pathogen antigen or an antigenic determinant thereof.

70. The method as claimed in claim 68, wherein the polynucleotides are administered in or on a particle or particles.

71. The method as claimed in claim 70, wherein the polynucleotide coding for a modulator of Notch signalling and the polynucleotide coding for

the antigen or antigenic determinant thereof are administered in or on the same or separate particles.

72. (canceled)

73. The method as claimed in claim 68, wherein the particle is administered directly into skin or muscle tissue, to mucosal tissue, by inhalation, or topically.

74-76. (canceled)

77. A particle acceleration device suitable for use for biolistic delivery, wherein said device is **loaded** with particles as claimed in claim 1.

78. A polynucleotide conjugate comprising first and second polynucleotide sequences, wherein the first sequence is a polynucleotide for Notch signaling modulation or codes for a polypeptide for Notch signalling modulation and the second sequence encodes an antigen or antigenic determinant.

79. The polynucleotide conjugate as claimed in claim 78 in the form of a vector.

80. (canceled)

81. (canceled)

82. The polynucleotide conjugate as claimed in claim 78, wherein the first polynucleotide sequence codes for: (i) a Notch ligand or a fragment, derivative, homologue, analogue or allelic variant thereof; (ii) a protein or polypeptide which comprises a Notch ligand DSL domain and at least one Notch ligand EGF-like domain; (iii) a protein or polypeptide which comprises a Notch ligand DSL domain, at least two Notch ligand EGF-like domains, and optionally a membrane binding or transmembrane domain.

83. The polynucleotide conjugate as claimed in claim 82, wherein the Notch ligand is Delta or Serrate/Jagged protein or a fragment, derivative, homologue, analogue or allelic variant thereof.

84. (canceled)

85. (canceled)

86. The polynucleotide conjugate as claimed in claim 78, wherein the first and second sequences are operably linked to one or more promoters.

87. The polynucleotide conjugate as claimed in claim 86, wherein the first and second sequences are operably linked to one or more enhancers.

88. The polynucleotide conjugate as claimed in claim 78, wherein the first sequence is operably linked to a first promoter and the second sequence is operably linked to a second promoter.

89. The polynucleotide conjugate as claimed in claim 78, wherein the first and second sequences are operably linked to one or more polyadenylation sequences.

90. The polynucleotide conjugate as claimed in claim 78 for expression in mammalian cells.

91. The polynucleotide conjugate as claimed in claim 78 comprising a selection marker.

92-94. (canceled)

95. A vaccine composition comprising the particle as claimed in claim 1.

L26 ANSWER 3 OF 54 USPATFULL on STN
2006:196135 Mediators of reverse cholesterol transport for the treatment of hypercholesterolemia.
Sircar, Jagadish C., San Diego, CA, UNITED STATES
Alisala, Kashinatham, San Diego, CA, UNITED STATES
Nikoulin, Igor, San Diego, CA, UNITED STATES
US 2006166891 A1 20060727
APPLICATION: US 2004-829855 A1 20040422 (10)
PRIORITY: US 2003-464667P 20030422 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A mediator of reverse cholesterol transport comprising a molecule comprising an acidic region, a lipophilic or aromatic region and a basic region, said molecule having a structure adapted to complex with HDL and/or low density lipoproteins-cholesterol (LDL) and thereby enhance reverse cholesterol transport.

2. The mediator of reverse cholesterol transport of claim 1, wherein said molecule has between 3 and 10 amino acid residues or analogs thereof, and comprises the sequence: X1--X2--X3, wherein X1 is an acidic amino acid, X2 is a lipophilic or aromatic amino acid, and X3 is a basic amino acid, and wherein X1, X2 and X3 may be arranged in any sequential order; wherein an amino terminal further comprises a first protecting group selected from the group consisting of an acetyl, phenylacetyl, pivolyl, 9-fluorenylmethyloxycarbonyl, 2-napthylic acid, nicotinic acid, a CH_3--$(CH_2)_n$--CO-- where n ranges from 3 to 20, di-tert-butyl-4-hydroxy-phenyl, naphthyl, substituted naphthyl, f-MOC, biphenyl, substituted phenyl, substituted heterocycles, alkyl, aryl, substituted aryl, cycloalkyl, fused cycloalkyl, saturated heteroaryl, and substituted saturated heteroaryl; and wherein a carboxy terminal further comprises a second protecting group selected from the group consisting of an amine, such as RNH_2 where R=H, di-tert-butyl-4-hydroxy-phenyl, naphthyl, substituted naphthyl, f-MOC, biphenyl, substituted phenyl, substituted heterocycles, alkyl, aryl, substituted aryl, cycloalkyl, fused cycloalkyl, saturated heteroaryl, and substituted saturated heteroaryl.

3. The mediator of reverse cholesterol transport of claim 2, wherein one or more of X1, X2 or X3 are D amino acid residues.

4. The mediator of reverse cholesterol transport of claim 2, wherein one or more of X1, X2 or X3 are modified synthetic or semisynthetic amino acids.

5. The mediator of reverse cholesterol transport of claim 4, wherein the modified synthetic or semi-synthetic amino acid is biphenylalanine.

6. A substantially pure amino acid-derived substance for treating and/or preventing hypercholesterolemia and/or atherosclerosis in a mammal, said substance having an amino and a carboxy terminal and comprising an L or D enantiomer of an acidic amino acid residue or derivative thereof, an L or D enantiomer of a lipophilic or aromatic amino acid residue or derivative thereof, and an L or D enantiomer of a basic amino acid

residue or derivative thereof, wherein the amino terminal further comprises a first protecting group selected from the group consisting of an acetyl, phenylacetyl, pivolyl, 9-fluorenylmethyloxycarbonyl, 2-napthylic acid, nicotinic acid, a $CH_3--(CH_2)n--CO--$ where n ranges from 3 to 20, di-tert-butyl-4-hydroxy-phenyl, naphthyl, substituted naphthyl, f-MOC, biphenyl, substituted phenyl, substituted heterocycles, alkyl, aryl, substituted aryl, cycloalkyl, fused cycloalkyl, saturated heteroaryl, substituted saturated heteroaryl, and the like; wherein the carboxy terminal further comprises a second protecting group selected from the group consisting of an amine, such as RNH_2 where R=H, di-tert-butyl-4-hydroxy-phenyl, naphthyl, substituted naphthyl, f-MOC, biphenyl, substituted phenyl, substituted heterocycles, alkyl, aryl, substituted aryl, cycloalkyl, fused cycloalkyl, saturated heteroaryl, substituted saturated heteroaryl, and the like; and wherein said substance has at least one of the following properties: (1) it mimicks ApoA-I binding to LDL and HDL, (2) it binds preferentially to liver, (3) it enhances LDL uptake by liver LDL-receptors, (4) it lower the levels of LDL, IDL, and VLDL cholesterol, (5) it increases the levels of HDL cholesterol, and (6) it enhances plasma lipoprotein profiles.

7. A composition suitable for oral administration that ameliorates or prevents a symptom of hypercholesterolemia, wherein said composition comprises an amino acid-derived molecule having an acidic region, a lipophilic or aromatic region and a basic region, and wherein said amino acid-derived molecule has a first protecting group attached to an amino terminal and a second protecting group attached to a carboxyl terminal, and wherein said amino acid-derived molecule optionally comprises at least one D amino acid residue.

8. The composition of claim 7, which includes at least one D amino acid residue

9. A peptide mediator of RCT, comprising the sequence: $Xa--Xb--(X1--X2--X3)--Xc--Xd$, wherein Xa is an acylated amino acid residue; Xb is any 0-10 amino acid residues; X1--X2--X3 are amino acid residues or derivatives thereof selected independently from an acidic amino acid residue, a lipophilic amino acid residue, and a basic amino acid residue or derivative thereof, with the proviso that one of said X1, X2 or X3 is an acidic residue, one of said X1, X2 or X3 is a lipophilic residue and one of said X1, X2 or X3 is a basic residue; Xc is any 0-10 amino acid residues; Xd is an amidated amino acid residue; and wherein the peptide mediator has 15 or fewer amino acid residues and optionally comprises at least one D amino acid residue.

10. An RCT mediator, comprising a compound selected from the group consisting of the synthetic compounds 1-96 of Table 5.

11. An RCT mediator, comprising a compound selected from the group consisting of SEQ ID NOS: 1 and 107-117.

12. An RCT mediator, comprising a compound selected from the group consisting of SEQ ID NOS: 1, 26-36, 42, 45-47, 56-58, 68-70, 72-74, 76, 80, 81, 83-90 and 92-95.

13. A pharmaceutical composition comprising SEQ ID NO: 1.

14. A pharmaceutical composition comprising SEQ ID NO: 113.

15. A pharmaceutical composition comprising SEQ ID NO: 34.

16. A pharmaceutical composition comprising SEQ ID NO: 86.

17. A pharmaceutical composition comprising SEQ ID NO: 91.

18. A pharmaceutical composition comprising SEQ ID NO: 96.

19. A pharmaceutical composition comprising SEQ ID NO: 145.

20. A pharmaceutical composition comprising SEQ ID NO: 146.

21. A pharmaceutical composition comprising SEQ ID NO: 118.

22. A method for treating or preventing hypercholesterolemia and/or atherosclerosis, comprising administering to a mammal in need thereof an amount of a composition selected from the group consisting of SEQ ID NOS: 1-176 (Table 3) and synthetic compounds 1-96 (Table 5), wherein said amount is sufficient to enhance RCT and/or cause regression of existing atherosclerotic lesions or reduce formation of said lesions.

23. A method for treating or preventing hypercholesterolemia and/or atherosclerosis, comprising administering to a mammal in need thereof an amount of a composition selected from the group consisting of SEQ ID NOS: 1, 113, 34, 86, 91, 96, 145, 146, and 118, wherein said amount is sufficient to enhance RCT and/or cause regression of existing atherosclerotic lesions or reduce formation of said lesions.

24. The method of claim 22, wherein administering is via an oral route.

25. The method of claim 22, wherein administering is combined with administration of a bile acid-binding resin, niacin, a statin, or a combination thereof.

26. An in vitro screening method for identifying test compounds that are likely to enhance reverse cholesterol transport in vivo, comprising: measuring cholesterol accumulation in liver cells in vitro in the presence and absence of the test compounds; measuring cholesterol accumulation and/or efflux in AcLDL-**loaded** **macrophages** in vitro in the presence and absence of test compounds; and identifying test compounds that enhance cholesterol accumulation in liver cells and reduce cholesterol levels in **macrophages**.

27. The in vitro screening method of claim 26, further comprising measuring cholesterol levels in OxLDL-**loaded** vascular smooth muscle cells in vitro in the presence and absence of test compounds, and wherein the step of identifying test compounds further comprises identifying compounds that enhance cholesterol accumulation in liver cells and reduce cholesterol levels in **macrophages** and/or reduce cholesterol levels in vascular smooth muscle cells.

28. The in vitro screening method of claim 26, wherein said liver cells are human HepG2 hepatoma cells.

29. The in vitro screening method of claim 26, wherein said **macrophages** are human THP-1 cells.

30. The in vitro screening method of claim 27, wherein said vascular smooth muscle cells are primary aortic smooth muscle cells.

31. An in vitro screening method for identifying test compounds that are likely to enhance reverse cholesterol transport in vivo, comprising: measuring cholesterol accumulation in liver cells in vitro in the presence and absence of the test compounds; measuring cholesterol

levels in AcLDL-**loaded** vascular smooth muscle cells in vitro in the presence and absence of test compounds; and identifying test compounds that enhance cholesterol accumulation in liver cells and reduce cholesterol levels in vascular smooth muscle cells.

L26 ANSWER 4 OF 54 USPATFULL on STN
2006:188716 Method to measure a t cell response and its uses to qualify antigen-presenting cells.
Abastado, Jean-Pierre, Paris, FRANCE
Bercovici, Nadege, Paris, FRANCE
Ernstoff, Marc S., Us-Hanover, NH, UNITED STATES
Givan, Alice L., Us-Durham, NH, UNITED STATES
Nardin, Alessandra, Paris, FRANCE
Magguilli born Salcedo, Margarita, Chatillon, FRANCE
Wallace, Paul K., Orchard Park, NY, UNITED STATES
US 2006160153 A1 20060720
APPLICATION: US 2003-537500 A1 20031202 (10)
WO 2003-EP13579 20031202 20051202 PCT 371 date
PRIORITY: US 2002-430347P 20021203 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1-49. (canceled)

50. A method to characterize a T-cell response of a final population of T-lymphocytes resulting from the co-incubation of an initial population of T lymphocytes with a composition of purified antigen-presenting cells (APCs), said method comprising the following steps: 1. the simultaneous measure on a single cell basis of at least two parameters: i. the first parameter being necessarily proliferation of T lymphocytes, ii. the second parameter being necessarily chosen among the group consisting of presence of a T cell antigen receptor on the surface of T lymphocytes and presence of at least one biological molecule produced by T lymphocytes, and the attribution of a positive or a negative value to each of these parameters, 2. the classification of the final T-lymphocytes population into 2n different subsets of T lymphocytes, n being the number of parameters used for the measure, each subset being characterized by a positive or a negative value respectively to each parameter, and the determination of the proportion of T lymphocytes present in each subset with respect to the number of T lymphocytes in the final population, with said proportion being characteristic of the T-cell response.

51. The method according to claim 1, further comprising evaluating said parameters as part of a potency assay for a composition of purified APCs or a method to evaluate the effect, on a T-cell response, of one or more cytokines secreted by a composition of purified APCs or a method to evaluate the effect, on a T-cell response, of one or more surface determinant markers present on T-cells or a batch release assay of a composition of purified APCs or an inclusion criterion for a patient wherein the composition of purified APCs originating from said patient have the ability to induce a proliferation of T lymphocytes, resulting in a proliferation index at least greater than 2, more preferably of at least 5, more preferably of at least 10, more preferably of at least 15, more preferably of at least 20, more preferably of at least 30, more preferably of at least 50 or an antigen selecting assay wherein the antigen to be tested is **loaded** on purified APCs and the T lymphocyte response triggered by the co-incubation with said **loaded** purified APCs is compared to the T lymphocyte response induced by a composition of purified APCs **loaded** with reference antigen or method to define a standard control T-cell response of

T-lymphocytes comprising: the co-incubation of an initial population of T-lymphocytes with different compositions of purified APCs presenting different concentrations of an antigen or of an antigen fragment of interest or of a reference antigen or of a fragment of reference antigen and, the determination of the variation of the degree of proliferation of said T-lymphocytes measured for each composition of purified APCs according the quantity of said antigen or said fragment of antigen of interest or said reference antigen or said fragment of reference antigen.

52. The method according to claim 51, wherein the step (1) of said method comprises the measure of an additional parameter being the presence or not of at least one surface determinant marker on T lymphocytes, different from T cell antigen receptors.

53. The method according to claim 53, wherein purified antigen-presenting cells are **loaded** with at least one antigen or fragment of antigen.

54. The method according to claim 53, wherein the T cell antigen receptor on the surface of T lymphocytes is specific or not for an antigen or fragment of antigen **loaded** on said purified APCs.

55. The method according to claim 54, wherein the T cell antigen receptor on the surface of T lymphocytes is specific for an antigen or of a fragment of antigen **loaded** on said purified APCs.

56. The method according to claim 51, wherein said method comprises a third step of determination, from the proportion of T lymphocytes in each of the different subset present in the final population, of the proportion of T lymphocytes in each corresponding subset present in the initial population with respect to the number of T lymphocytes in the initial population.

57. The method according to claim 56, wherein the determination of the proportion of T lymphocytes present in the initial population of T-lymphocytes **loaded** with a fluorescent probe allowing the measure of proliferation is made according to following steps: (i) marking n minus 1 parameters, the parameter corresponding to the proliferation being previously marked, with fluorescent probes specific for each of the n minus 1 parameters, (ii) gating T-lymphocytes in the final population of T lymphocytes according to the fluorescence of the n minus 1 chosen parameters, the measure of proliferation being excluded at this step, the value of which define lymphocytes subsets of interest, (iii) building a fluorescent curve by recording the fluorescence intensity of the probe used to measure proliferation of the T-lymphocytes gated at step (ii), (iv) possibly building a fluorescent curve by recording the fluorescence intensity of the probe used to measure proliferation from either: (iva) T-lymphocytes present in a lymphocytes subset defined by gating lymphocytes in the final population of T lymphocytes according to the absence of fluorescence of the n minus 1 chosen parameters or, (ivb) T-lymphocytes present in a sample of T-lymphocytes of the initial population not co-incubated with purified APCs, (v) determining intensity of fluorescence of non-proliferating lymphocytes by analyzing the distribution of fluorescence of the fluorescent curve built at step (iii), or possibly at step (iv), the non-proliferating lymphocytes corresponding to the maximal value of fluorescence, (vi) deriving, from the fluorescence curve recorded at step (iii), Gaussian curves centered on successive half intensity values derived from the maximal intensity of fluorescence determined from non-proliferating T-lymphocytes at step (iii) or at step (iv), to obtain Ak which is the proportion of cells in division k at the time of the measure of the proliferation,

(vii) determining the proportion of T-lymphocytes (PF=precursor frequency) in the initial population that have proliferated in order to give the proportion of T lymphocytes present in the selected subset (step ii) using the formula: ##EQU8## wherein PF is precursor frequency in the initial population, Ak is the proportion of cells in division k at the time of the measure of the proliferation, k=0 for initial population of T lymphocytes, and cells having undergone 2 to n divisions having been classified as proliferating T lymphocytes, (viii) determining the percentage of non-proliferating T-lymphocytes from the percentage of T-lymphocytes that have not proliferated and that are present in the final population of T-lymphocytes and half the percentage of T-lymphocytes that had undergone only one cell division, (ix) applying the percent of non-proliferating T-lymphocytes to the number of gated T-lymphocytes in the data file to give the absolute number of T-lymphocytes in the corresponding subset before culture that will not proliferate according to the formula, numbernon-proliferating cells in the initial population[(proportioncells that have not proliferated and that are present in the sample at the end of the experiment)+(0.5*proportioncells that have divided only once and that are present in the sample at the end of the experiment)]*[numbergated cells in data file]) (x) determining the absolute number of T-lymphocytes in the corresponding subset destined to divide by knowing the number of T-lymphocytes that was not destined to divide and the number of precursor cells of proliferating T-lymphocytes according to the formula, numberproliferating cells in the initial population=[(PFproliferating cells)*(numbernon-proliferating cells in the initial population)]/[1-PFproliferating cells], (xi) reiterating step (i) to step (viii) to each T lymphocytes subsets determined according to the n parameters used for the measure, (xii) summation of number of cells in the 2n subsets in order to express the number of T-lymphocytes present in the initial population of T-lymphocytes as a percentage of the total initial population before co-incubation.

58. The method according to claim 51, wherein purified APCs are purified **monocyte**-derived antigen presenting cells.

59. The method according to claim 51, wherein purified APCs are purified immature, maturing or mature dendritic cells, **monocytes** or **macrophages**.

60. The method according to claim 53, wherein purified APCs are **loaded** with at least one antigen or a fragment of antigen which is an antigen of tumoral or infectious origin.

61. The method according to claim 60, wherein said antigen is comprised in the group consisting of: EBV, CMV, HBV, p53, tetanus toxin, Melan-A/MART-1, MAGE-3, MAGE-2, PSA, PSMA, PAP, HSP70, CEA, Ep-CAM, MUC1, MUC2, HER2/neu, M1 protein from the influenza virus, or peptides derived from these proteinic antigens.

62. The method according to claim 51, wherein co-incubation of purified APCs and T lymphocytes lasts for a time sufficient to allow at least 1 division of T lymphocytes, preferably 5 divisions.

63. The method according to claim 62, wherein co-incubation lasts from 1 to 10 days, and more preferably 4 to 10 days.

64. The method according to claim 51, wherein co-incubation comprises a step of adding a T lymphocyte stimulating agent at the end of the co-incubation period.

65. The method according to claim 51, wherein proliferation of T

lymphocytes is measured by using a probe **loaded** into T lymphocytes before or concomitantly to the step of co-incubation, said probe being substantially equally distributed between dividing T-lymphocytes during cell division of T lymphocytes of the initial population.

66. The method according to claim 65, wherein the probe **loaded** before the co-incubation step is fluorescent and distributed in the cell membrane or inside the cytosol of T-lymphocytes.

67. The method according to claim 65, wherein the probe **loaded** into the T-lymphocytes concomitantly to the co-incubation step is a base analog that integrates into the DNA, such as BrdU.

68. The method according to claim 51, wherein the presence of a specific T cell antigen receptor on the surface of T lymphocytes is detected by using a detectable molecule having the ability to specifically bind to said T cell antigen receptor, such as a fluorescent tetramer.

69. The method according to claim 51, wherein the T cell antigen receptors on the surface of T lymphocytes are specific for an antigen from tumor or infectious origin.

70. The method according to claim 69, wherein said antigen is chosen among the group consisting of: EBV, CMV, HBV, M1 protein from the influenza virus, p53, tetanus toxin, Melan-A MART-1, MAGE-3, MAGE-2, PSA, PSMA, PAP, HSP70, CEA, Ep-CAM, MUC1, MUC2, HER2/neu, or peptides derived from these proteinic antigens.

71. The method according to claim 51, wherein the biological molecule whose presence is detected in final population of T lymphocytes, is a cytokine or a chemokine or an enzyme.

72. The method according to claim 71, wherein the cytokine is chosen among the group consisting of: IFN-γ, IL-2, IL-4, IL-5, IL-10.

73. The method according to claim 71, wherein the enzyme is chosen among the group consisting of perforine and granzyme.

74. The method according to claim 71, wherein the chemokine is chosen among the group consisting of a ligand for CCR5 and a ligand for CCR7.

75. The method according to claim 52, wherein the surface determinant marker of T-lymphocytes is chosen among the group consisting of CD4, CD8, CD28, CD69, CTLA-4, CD45-RA, CD45-RO, CD62-L.

76. The method according to claim 51, wherein the proportion of T lymphocytes in the different subsets of T lymphocytes in the final population and the proportion of T lymphocytes in the different corresponding subsets of T lymphocytes in the initial population are used to determine a proliferation index (PI) for each subset of T lymphocytes using the formula: ##EQU9## wherein Ak is the proportion of cells in division k

77. The method according to claim 51, wherein said method is used as a potency assay for a composition of purified APCs.

78. The method according to claim 77, wherein the purified APCs ability to activate T lymphocytes is characterized by the determination of the proliferation index and/or by the proportion of T lymphocytes precursors present in the initial population.

79. The method according to claim 28, wherein purified APCs are

characterized by their ability to induce proliferation of T lymphocytes, positive at least for the proliferation parameter, resulting in a proliferation index of at least 2, more preferably of at least 5, more preferably of at least 10, more preferably of at least 15, more preferably of at least 20, more preferably of at least 30, more preferably of at least 50.

80. The method according to claim 79, wherein purified APCs are characterized by their ability to induce a proliferation of T lymphocytes, positive at least for the proliferation parameter, resulting in a proliferation index ranging between 2 and 200, more particularly from 15 to 70, more particularly from 20 to 60, more particularly from 30 to 40 and more particularly from 20 to 200.

81. The method according to claim 51, wherein said method is used as a method to evaluate the effect, on a T-cell response, of one or more cytokines secreted by a composition of purified APCs.

82. The method according to claim 81, wherein the co-incubation of an initial population of T lymphocytes with a composition of purified antigen-presenting cells (APCs) takes place in the presence of an antibody able to bind specifically to a cytokine that is produced during co-incubation.

83. The method according to claim 82, wherein the cytokine is chosen among the group consisting of: IL-2, IL-10, IL-12, IL-15, IL-18, IL-23, TNF-α, TGF-β.

84. The method according to claim 51, wherein said method is used as a method to evaluate the effect, on a T-cell response, of one or more surface determinants markers present on T-cells.

85. The method according to claim 84, wherein the co-incubation of T-lymphocytes and purified APCs takes place in the presence of an antibody, or an antagonist, able to bind specifically to a surface determinant marker of T-lymphocytes.

86. The method according to claim 85, wherein the surface determinant marker is CD4, CD8, CD28, CTLA-4, B7, LFA-10, OX40-ligand, ICAM-1, 4-1BBL, DC-SIGN or MHC-II.

87. The method according to claim 51, wherein said method is used as a batch release assay of a composition of purified APCs.

88. The method according to claim 87, wherein purified APCs are characterized by the different percentages of T lymphocytes secreting a cytokine during the co-incubation.

89. The method according to claim 51, wherein said method is used as an inclusion criterion for a patient wherein the composition of purified APCs originating from said patient have the ability to induce a proliferation of T lymphocytes, resulting in a proliferation index at least greater than 2, more preferably of at least 5, more preferably of at least 10, more preferably of at least 15, more preferably of at least 20, more preferably of at least 30, more preferably of at least 50.

90. The method according to claim 54, wherein said method is used as an antigen selecting assay wherein the antigen to be tested is **loaded** on purified APCs and the T lymphocyte response triggered by the co-incubation with said **loaded** purified APCs is compared to the T lymphocyte response induced by a composition of purified APCs **loaded** with a reference antigen.

91. The method according to claim 90, wherein the reference antigen is chosen among the group consisting of: tetanus toxin, Melan-A, Flu peptide, PSA, and HIV.

92. The method according to claim 51, wherein said method is used to define a standard control T-cell response of T-lymphocytes comprising: the co-incubation of an initial population of T-lymphocytes with different compositions of purified APCs presenting different concentrations of an antigen or of an antigen fragment of interest or of a reference antigen or of a fragment of reference antigen and, the determination of the variation of the degree of proliferation of said T-lymphocytes measured for each composition of purified APCs according the quantity of said antigen or said fragment of antigen of interest or said reference antigen or said fragment of reference antigen.

93. The method according to claim 92, to evaluate the efficiency of a process for loading an antigen, or a fragment of antigen, into purified APCs wherein the efficiency of the said process is evaluated by comparing: a first response being a T-cell response of a final population of T-lymphocytes resulting from the co-incubation of an initial population of T-lymphocytes with a composition of purified APCs **loaded** with an antigen or a fragment of antigen, according to the process to be tested and, a second response being a standard control T-cell response of T-lymphocytes resulting from the co-incubation of an initial population of T-lymphocytes with different compositions of purified APCs **loaded** with different concentrations of said antigen or said fragment of antigen, or of a reference antigen, or of a fragment of reference antigen according to the process of reference, deducing from said comparison between said first and said second responses the difference of efficiency between the process to be tested and the process of reference.

94. The method according to claim 93, wherein the reference process is chosen among the group consisting of: fusion, electroporation, incubation, loading with liposomes, loading with virosomes, loading with exosomes or genetic engineering of antigen-presenting cells.

95. The method according to claim 92, to evaluate an impact of a method of an antigen preparation on the ability of an antigen-presenting cell to present antigen to T lymphocyte wherein the said method of preparation of antigen is evaluated by comparing: a first response being a T-cell response of a final population of T-lymphocytes resulting from the co-incubation of an initial population of T-lymphocytes with a composition of purified APCs **loaded** with an antigen or a fragment of antigen, prepared according to the method to be tested, a second response being a standard control T-cell response of T-lymphocytes resulting from the co-incubation of an initial population of T-lymphocytes with different compositions of purified APCs **loaded** with different concentrations of said antigen or said fragment of antigen, or of a reference antigen, or of a fragment of reference antigen, prepared according to a method of reference, deducing from said first and said second responses the impact of said method of antigen preparation to be tested on the ability of an antigen-presenting cell to present antigen to T lymphocyte.

96. The method according to claim 92 to evaluate stability of a presentation of an antigen (or fragment of antigen) by purified APCs wherein the said stability is evaluated by comparing: a first response being a T-cell response of a final population of T-lymphocytes resulting from the co-incubation of an initial population of T-lymphocytes with different compositions of purified APCs **loaded** with said antigen (or

fragment of antigen) said compositions of purified APCs being previously incubated in a medium not initially containing said antigen for different period of time and, a second response being a standard control T-cell response of T-lymphocytes resulting from the co-incubation of an initial population of T-lymphocytes with composition of purified APCs **loaded** with an antigen or a fragment of antigen, or a reference antigen, or a fragment of reference antigen said compositions of purified APCs being not previously incubated in a medium not initially containing said antigen or said fragment of antigen, or a reference antigen, or a fragment of reference antigen, deducing from the first and the second responses the stability of a presentation of said antigen (or fragment of antigen) by purified APCs.

97. The method according to claim 92, wherein the initial population of T lymphocytes is a clonal population or a cell line of T lymphocytes that is specific to the antigen, or fragment of antigen, presented in the context of MHC.

98. The method according to claim 92, wherein the initial population of T lymphocytes is an initial naive population of T lymphocytes, said initial naive population of T lymphocytes being substantially the same for obtaining a standard control T-cell response of T-lymphocytes and a T-cell response to be compared to said standard control T-cell response of T-lymphocytes.

L26 ANSWER 5 OF 54 USPATFULL on STN
2006:181499 Multi-compartment delivery system.
Ghabrial, Ragae, Helmetta, NJ, UNITED STATES
Fung, Ramie, Flemington, NJ, UNITED STATES
Rezania, Alireza, Hillsborough, NJ, UNITED STATES
Davis, Janet E., Branchburg, NJ, UNITED STATES
US 2006153894 A1 20060713
APPLICATION: US 2005-170410 A1 20050629 (11)
PRIORITY: US 2004-584343P 20040630 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A biocompatible, implantable, partially or fully biodegradable delivery device comprising at least two compartments, wherein said two compartments are prepared separately for delivering at least two distinct biological entities.

2. The device of claim 1, wherein said two compartments can be physically combined with each other in a manner that permits a biological entity to be **loaded** in one compartment to benefit from a biological entity to be **loaded** in the other compartment.

3. The device of claim 2, wherein one of said two compartments is a cellular compartment, and the other one is a compound compartment, and wherein said two compartments can be combined in such a manner to permit a compound to be **loaded** in said compound compartment to benefit proliferation, differentiation, survival or function of cells to be **loaded** in said cellular compartment.

4. The device of claim 2, wherein said two compartments are both cellular compartments, and wherein said two compartments can be combined in such a manner to permit cells to be **loaded** in one compartment to benefit proliferation, differentiation, survival or function of cells to be **loaded** in the other compartment.

5. The device of claim 3, wherein said compound compartment has been

loaded with a compound.

6. The device of claim 5, wherein said compound promotes attachment, proliferation or differentiation of cells **loaded** in an adjoining cellular compartment; or promotes extracellular matrix synthesis.

7. The device of claim 5, wherein said compound is selected from anti-rejection agents, angiogenic agents, analgesics, antioxidants, anti-apoptotic agents, or anti-inflammatory agents.

8. The device of claim 5, wherein said compound is selected from the group consisting of members of the TGF-β family, bone morphogenic proteins, fibroblast growth factors-1 and -2, platelet-derived growth factor-AA and -BB, platelet rich plasma, insulin growth factors), growth differentiation factors, vascular endothelial cell-derived growth factor (VEGF), exendin 4, **monocyte** chemoattractant protein-1 (MCP1), pleiotrophin, endothelin, nicotinamide, glucagon like peptide-I and II, parathyroid hormone, tenascin-C, tropoelastin, thrombin- derived peptides, laminin, biological peptides comprising cell- and heparin-binding domains of adhesive extracellular matrix proteins, and combinations thereof.

9. The device of claim 3 or claim 4, wherein said cellular compartment or compartments have been **loaded** with cells.

10. The device of claim 9, wherein said cells are selected from the group consisting of partially or fully differentiated glucose responsive insulin secreting cells, bone marrow cells, smooth muscle cells, stromal cells, stem cells, mesenchymal stem cells, synovial derived stem cells, embryonic stem cells, blood vessel cells, chondrocytes, osteoblasts, precursor cells derived from adipose tissue, bone marrow derived progenitor cells, kidney cells, intestinal cells, islets, beta cells, Sertoli cells, peripheral blood progenitor cells, fibroblasts, glomus cells, keratinocytes, nucleus pulposus cells, annulus fibrosus cells, fibrochondrocytes, stem cells derived from placenta, amniotic epithelium, amniotic fluid, umbilical cord, cord or cord blood, stem cells isolated from adult tissue, oval cells, neuronal stem cells, glial cells, **macrophages**, and combinations of the above.

11. The device of claim 2, wherein said two compartments are combined at the time of implantation.

12. The device of claim 3 or claim 4, wherein the cellular compartment or compartments are seeded with cells and are maintained in vitro for a period of time under appropriate culture conditions prior to implantation.

13. A method of treating a disease in a mammal, comprising implanting a biocompatible, partially or fully biodegradable delivery device which comprises at least two compartments, wherein said two compartments are prepared separately and are **loaded** separately with distinct biological entities that contribute to the treatment.

14. The method of claim 13, wherein said disease is insulin dependent diabetes.

L26 ANSWER 6 OF 54 USPATFULL on STN
2006:174015 Anticancer vaccine and diagnostic methods and reagents.
Finn, Olivera J., Pittsburgh, PA, UNITED STATES
Kao, Henry, St. Louis, MO, UNITED STATES
Hunt, Donald, Charlottesville, VA, UNITED STATES

Marto, Jarrod A., Charlottesville, VA, UNITED STATES
University of Pittsburgh of the Commonwealth System of Higher Education, Pittsburgh, PA, UNITED STATES (U.S. corporation)University of Virginia, Charlottesville, VA, UNITED STATES (U.S. corporation)
US 2006147460 A1 20060706
APPLICATION: US 2006-366196 A1 20060302 (11)
PRIORITY: US 2001-324450P 20010924 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A method for vaccinating a patient against malignancies comprising introducing a peptide comprises all or an immunogenic fragment of a cyclin protein into a patient under conditions sufficient for the patient to develop an immune response to the cyclin protein.

2. The method of claim 1, wherein the peptide consists essentially of all or an immunogenic fragment of a cyclin protein.

3. The method of claim 1, wherein the peptide comprises all or an immunogenic fragment of a cyclin A, D1, B1, or E protein.

4. The method of claim 1, wherein the peptide consists essentially of all or an immunogenic fragment of a cyclin A, D1, B1, or E protein.

5. The method of claim 1, wherein the peptide consists essentially of a mature cyclin B1 protein.

6. The method of claim 5, wherein the peptide has from 0 to about 5 single amino acid substitutions relative to a wild type sequence of about 10 amino acids.

7. The method of claim 1, wherein the peptide comprises a fragment of from about 5 to about 15 contiguous amino acids of a wild-type human cyclin B1 peptide.

8. The method of claim 7, wherein the peptide has from 0 to about 5 single amino acid substitutions relative to a wild type sequence of about 10 amino acids.

9. The method of claim 1, wherein the peptide consists essentially of a fragment of from about 5 to about 15 contiguous amino acids of a wild-type human cyclin B1 peptide.

10. The method of claim 9, wherein the peptide has from 0 to about 5 single amino acid substitutions relative to a wild type sequence of about 10 amino acids.

11. The method of claim 1, wherein the peptide comprises an amino acid sequence as set forth in SEQ ID NOs: 1-8.

12. The method of claim 1, wherein the peptide consists essentially of an amino acid sequence as set forth in SEQ ID NOs: 1-8.

13. A method of identifying tumor antigens comprising, obtaining naive CD4+ or CD8+ T cells from at least one healthy individual, obtaining at least one protein or peptide from at least one cancerous cell; obtaining antigen presenting cells (APCs), culturing the APCs with the at least one protein or peptide, and adding the T cells to the culture of the APCs, whereby the T cells are primed against the at least one protein or peptide, and assessing the peptide sequence of the stimulatory molecules.

14. The method of claim 13, wherein the T cells are CD4+ T cells.

15. The method of claim 13, wherein the at least one protein or peptide is obtained by lysing the cancerous cell to obtain a lysate and extracting the protein or peptide from the lysate.

16. The method of claim 13, wherein the T cells are CD8+ T cells.

17. The method of claim 13, wherein the at least one protein or peptide is obtained by extracting HLA class I molecules from the cancerous cell and eluting the protein or peptide from the extracted HLA class I molecules.

18. The method of claim 13, wherein the at least one protein or peptide is fractionated.

19. The method of claim 13, wherein the at least one protein or peptide is obtained from a tumor comprising the at least one cancerous cell.

20. The method of claim 13, wherein the APCs are dendritic cells.

21. The method of claim 20, wherein the dendritic cells are generated in vitro.

22. The method of claim 13, wherein the APCs are cultured with the at least one protein or peptide in the presence of tumor necrosis factor α.

23. The method of claim 13, wherein the T cells are added to the culture of the APCs in the presence of one or more cytokines.

24. The method of claim 23, wherein the cytokines are selected from the group of cytokines consisting of IL-1β, IL-2, and IL-4, and IL-7.

25. The method of claim 13, wherein the T cell/APC culture is restimulated by introducing autologous **macrophages**, **loaded** with the at least one protein or peptide, or irradiated cancerous cells.

26. The method of claim 13, wherein the T cell/APC culture is restimulated more than one time at intervals of from about 7 to about 10 days.

L26 ANSWER 7 OF 54 USPATFULL on STN
2006:166478 Dendritic cells loaded with heat shocked melanoma cell bodies.
Palucka, Anna Karolina, Dallas, TX, UNITED STATES
Banchereau, Jacques, Dallas, TX, UNITED STATES
Baylor Research Institute, Dallas, TX, UNITED STATES (U.S. corporation)
US 2006140983 A1 20060629
APPLICATION: US 2005-257951 A1 20051025 (11)
PRIORITY: US 2004-621957P 20041025 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A composition for inducing immunity to cancer in a patient comprising isolated and purified antigen presenting cells primed by exposure to one or more heat-shocked and killed cancer cells.

2. The composition of claim 1, wherein the antigen presenting cells comprise dendritic cells.

3. The composition of claim 1, wherein the antigen presenting cells are

loaded with heat-shocked, heat-killed cancer cells.

4. The composition of claim 1, wherein the cancer cells are isolated from a patient.

5. The composition of claim 1, wherein the cancer cells comprise allogeneic cancer cells.

6. The composition of claim 1, wherein the heat-shocked and killed cancer cells are internalized and processed by the antigen presenting cells for at least 2 hours.

7. The composition of claim 1, wherein the cancer cell comprises one or more tumor cell lines.

8. A method of inducing immunity to cancer in a patient comprising the steps of: heat-shocking one or more cancer cells at a temperature of at least about 42° C. for at least two hours to form heat shocked cancer cells; killing the heat shocked cancer cells to form heat shocked, killed cancer cells; incubating one or more antigen presenting cells isolated from the patient with the heat shocked, killed cancer cells for at least three hours; and administering one or more isolated, **loaded** antigen presenting cells to the patient.

9. The method of claim 8, wherein the antigen presenting cells are matured with one or more cytokines prior to administering to the patient.

10. The method of claim 8, wherein the antigen presenting cells are dendritic cells.

11. The method of claim 8, wherein the cancer cell comprises one or more tumor cell lines.

12. A method of inducing immunity to cancer in a patient comprising the steps of: obtaining antigen presenting cells from the patient; incubating allogeneic cancer cells at a temperature of at least 42° C. for at least two hours to form heat shocked allogeneic cancer cells; killing the heat shocked allogeneic cancer cells to form heat shocked, killed allogeneic cancer cells; exposing the antigen presenting cells to the heat shocked, killed allogeneic cancer cells for at least three hours to form **loaded** antigen presenting cells; maturing the isolated, **loaded** antigen presenting cells; and administering the isolated, **loaded** antigen presenting cells to the patient.

13. The method of claim 12, wherein the antigen presenting cells comprise dendritic cells.

14. The method of claim 12, wherein the heat shocked, killed cancer cells are internalized by the antigen presenting cells and the antigen presenting cells are matured with one or more cytokines.

15. The method of claim 12, wherein the cancer cells are selected from Table II.

16. A method of preparing immunogenic isolated antigen presenting cells comprising the steps of: isolating antigen presenting cells from a subject; preparing an antigen by stressing one or more cancer cells and killing the cancer cells; loading the antigen presenting cells with the antigen for at least three hours; and isolating and purifying the **loaded** antigen presenting cells.

17. The method of claim 16, wherein the cancer cells are stressed by a method selected from the group consisting of heat shock, cold shock, glucose deprivation, oxygen deprivation, exposure to at least one drug that alter cell metabolism, and exposure to at least one cytotoxic drug prior to killing the cancer cells.

18. The method of claim 16, wherein the cancer cells are allogeneic cancer cells.

19. The method of claim 16, wherein the step of loading the antigen presenting cells with the antigen is conducted under heat shock.

19. A method of increasing the expression of tumor antigens in stressed and killed cancer cells comprising stressing the cancer cells prior to killing the cancer cells.

20. The method of claim 19, wherein the cancer cells are stressed by a method selected from the group consisting of heat shock, cold shock, glucose deprivation, oxygen deprivation, exposure to at least one drug that alter cell metabolism, and exposure to at least one cytotoxic drug prior to killing the cancer cells.

21. A method of increasing the antigenicity of tumor antigens in antigen presenting cells **loaded** with stressed and killed cancer cells comprising stressing the cancer cells and killing the cancer cells and exposing the antigen presenting cells to the stressed and killed cancer cells.

22. The method of claim 21, wherein the cancer cells are stressed by a method selected from the group consisting of heat shock, cold temperature, glucose deprivation, oxygen deprivation, exposure to at least one drug that alters cell metabolism, and exposure to at least one cytotoxic drug prior to killing the cancer cells.

23. An antigen comprising heat shocked cancer cells and portions thereof.

24. A method of preparing an antigen comprising heat-treating one or more cancer cell lines and killing the cells with one or more cell death inducing agents.

25. The method of claim 24, wherein the cell death inducing agents comprises betulinic acid, paclitaxel, camptothecin, ellipticine, mithramycin A, etoposide, vinblastine, vincristine, ionomycin and combinations thereof.

26. The method of claim 24, wherein the cell death inducing agents comprises radiation, heat, cold, osmotic shock, pressure, grinding, shearing, ultrasound, drying, freeze spraying, puncturing, starving and combinations thereof.

27. The method of claim 24, wherein the cancer cell is selected from Table II.

28. The method of claim 24, wherein the cancer cell is heat treated for 2, 4, 6 or 8 hours.

29. The method of claim 24, wherein the cancer cell is defined further as comprising a hot melanoma and portions thereof.

30. An antigen comprising heat-shocked and killed cancer cells and

portions thereof.

31. The antigen of claim 30, wherein the antigen is lyophilized, heat-dried, vacuum dried, heat-vacuum dried, frozen by evaporative precipitation into aqueous solution (EPAS), spray freezing into liquid (SFL), antisolvent precipitation or freeze spraying.

32. The antigen of claim 30, further comprising an adjuvant.

33. The antigen of claim 30, wherein the heat shocked cancer cells and portions thereof are killed by betulinic acid, paclitaxel, camptothecin, ellipticine, mithramycin A, etoposide, vinblastine, vincristine, ionomycin and combinations thereof.

34. The antigen of claim 30, wherein the heat shocked cancer cells and portions thereof are killed by radiation, heat, cold, osmotic shock, pressure, grinding, shearing, ultrasound, drying, freeze spraying, puncturing, starving and combinations thereof.

35. A vaccine comprising killed, allogeneic cancer cells heat-shocked at a temperature of at least 42° C. for at least two hours to form heat shocked, killed allogeneic cancer cells.

36. A cancer vaccine made by a method comprising the steps of: incubating at a temperature of at least 42° C. for at least two hours cancer cells; killing the heat shocked cancer cells; and loading antigen presenting cells with the heat-shocked and killed cancer cells.

37. The vaccine of claim 36, adapted for administration of the isolated, **loaded** antigen presenting cells to the patient.

38. A cancer vaccine for use in a patient comprising one or more at least partially mature antigen presenting cells **loaded** with heat shocked and killed cancer cells that are non-apoptotic.

39. A method of treating a cancer patient comprising: immunizing the patient with a cancer vaccine comprising one or more at least partially mature antigen presenting cells **loaded** with heat shocked and killed cancer cells that are non-apoptotic.

40. The method of claim 39, wherein the one or more at least partially mature antigen presenting cells are autologous.

41. The method of claim 39, wherein the heat shocked and killed cancer cells are autologous.

42. The method of claim 39, heat shocked and killed cancer cells selected from the cells in Table II.

43. The method of claim 39, wherein the HSP60, HSP90 and gp96 of the cancer cells are upregulated prior to killing.

44. The method of claim 39, wherein the cancer cells are transfected to overexpress HSP60, HSP90 and gp96.

45. The method of claim 39, wherein the cancer cells are killed by betulinic acid, paclitaxel, camptothecin, ellipticine, mithramycin A, etoposide, vinblastine, vincristine, ionomycin and combinations thereof.

46. The method of claim 39, wherein the cancer cells are killed by radiation, heat, cold, osmotic shock, pressure, grinding, shearing, ultrasound, drying, freeze spraying, puncturing, starving and

combinations thereof.

47. A method of delivering antigen to dendritic cells in vitro comprising: contacting dendritic cells capable of internalizing one or more antigens for antigen presentation for a time sufficient to allow the one or more antigens to be internalized for presentation to immune cells, wherein the antigen comprises heat-shocked and killed cancer cells.

48. The method of claim 47, wherein the dendritic cells are human.

49. The method of claim 47, wherein the heat-shocked cells are selected from the group consisting of cell lines, cells transformed to express a foreign antigen, tumor cell line, xenogeneic cells, or tumor cells.

50. The method of claim 47, wherein the heat-shocked cells are selected from the group consisting of the cell lines listed in Table II and combinations thereof.

51. The method of claim 47, wherein the cells are killed by chemical treatment, radiation, heat, cold, osmotic shock, pressure, grinding, shearing, ultrasound, drying, freeze spraying, puncturing, starving and combinations thereof.

52. The method of claim 47, wherein the dendritic cells are exposed to a preparation of heat-shocked, apoptotic cell fragments, blebs, or bodies comprising antigen.

53. The method of claim 47, wherein the dendritic cells are immature and **phagocytic**.

54. The method of claim 47, wherein the cancer cells are killed by apoptosis.

55. The method of claim 47, wherein the ratio of heat-shocked cells to dendritic cells is about 1-10 heat-shocked cells to about 100 dendritic cells.

56. The method of claim 47, further comprising a maturation step wherein the dendritic cells are exposed to a maturation factor for a sufficient time to induce maturation of the dendritic cells.

57. The method of claim 47, wherein the maturation step comprises contacting CD83 negative dendritic cells with at least one maturation factor selected from the group consisting of **monocyte** conditioned medium that causes CD83 negative dendritic cells to mature so as to express CD83, TNFα, IL-1β, IL-6, PGE2, IFNα, CD40 ligand, and heat-shocked and killed cells.

58. The method of claim 47, wherein the maturation factor is selected from the group consisting of **monocyte** conditioned medium; IFNα and at least one other factor selected from the group consisting of IL-1β, IL-6 and TNFα; and heat-shocked cells.

59. The method of claim 47, wherein the antigen is a tumor cell that further comprises a virus.

60. The method of claim 47, wherein the dendritic cells are CD83 negative dendritic cells while contacting the antigen.

L26 ANSWER 8 OF 54 USPATFULL on STN

2006:159065 Polymer affinity matrix, a method for the production and use thereof.
Rapp, Wolfgang, Tubingen, GERMANY, FEDERAL REPUBLIC OF
Deppisch, Reinhold, Hechingen, GERMANY, FEDERAL REPUBLIC OF
Gohl, Hermann, Bisingen, GERMANY, FEDERAL REPUBLIC OF
Wittner, Bernd, Hechingen, GERMANY, FEDERAL REPUBLIC OF
Beck, Werner, Rottenburg, GERMANY, FEDERAL REPUBLIC OF
US 2006134595 A1 20060622
APPLICATION: US 2003-520532 A1 20030704 (10)
WO 2003-SE1166 20030704 20050927 PCT 371 date
PRIORITY: SE 2002-114 20020708
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A polymer affinity matrix comprising a) a solid support b) at least one spacer bound to the solid support, and, coupled to each spacer, c) at least one ligand containing at least one binding unit having at least one functional group, wherein the polymer affinity matrix has the ability to selectively bind to at least one substance in a fluid.

2. The polymer affinity matrix according to claim 1, wherein said at least one ligand has a defined three-dimensional structure which is complementary as regards charge and/or hydrophobicity/hydrophilicity to the three-dimensional structure of a binding motif of said at least one substance.

3. The polymer affinity matrix according to claim 1, wherein the at least one ligand is represented with the formula --X1n--Ym[X2i-Z1; X3j-Z2]1/2(m+1), (general Formula I), wherein n=0 or 1; m=2k.about.1; k=0 to 10, wherein if k=0 then X2.dbd.X3 and Z1=Z2; i=0 or 1; and j=0 or 1, or --(X1n--Y1[Y2m[X2i-Z1; X3j-Z2]1/2(m+1))r--X4p-Z3, (general Formula II), wherein n=0 or 1; m=2k-1; k=0-10, wherein if k=0 then X2=X3 and Z1=Z2; r=1-100; i=0 or 1; j=0 or 1; and p=0 or 1; wherein Z1, Z2 and Z3 each independently of each other represents the at least one binding unit and each is an organic molecule chosen from amino acids, peptides, fatty acids, carbohydrates, lectin, and nucleotides, and derivatives thereof, and combinations thereof, wherein Y, Y1 and Y2 each is independently of each other a trifunctional branching molecule chosen from amino, hydroxy, aldehyde, isocyanate, isotiocyanate, thiol, maleimido, and epoxy, and derivatives thereof, and combinations thereof, and wherein X1, X2, and X3 each, is independently of each other, an optional bifunctional distance molecule containing two functional groups chosen from amino, carboxy, hydroxy, aldehyde, isocyanate, isothiocyanate, thiol, maleimido, and epoxy, and derivatives thereof, and combinations thereof; wherein optionally the ligand is cyclic.

4. The polymer affinity matrix according to claim 1, wherein the at least one ligand comprises 1 to 100 functional groups.

5. The polymer affinity matrix according to claim 1, wherein the at least one binding unit is an amino acid, at least a part of which is positively charged at about physiological pH of blood.

6. The polymer affinity matrix according to claim 5, wherein the amino acid has a pKA of ≥6.0.

7. The polymer affinity matrix according to claim 6, wherein the amino acid is arginine, lysine, histidine, or cysteine.

8. The polymer affinity matrix according to claim 7, wherein the amount or concentration of the amino acid is 0.01 to 5 mmol/g matrix.

9. The polymer affinity matrix according to claim 8, wherein the amount or concentration of the amino acid is chosen from 0.01, 0.1, 1, 2, 3, 4 and 5 mmol/g matrix.

10. The polymer affinity matrix according to claim 5, wherein the number of amino acid molecules per ligand is chosen from 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 and 16.

11. The polymer affinity matrix according to claim 5, wherein the amino acid is arginine and the concentration of arginine is ≤3 mmol/g matrix.

12. The polymer affinity matrix according to claim 1, wherein said at least one functional group is chosen from amino group or substituted amino group, a carboxy group, a hydroxy group, a thiol group, a guanidino group, and combinations thereof.

13. The polymer affinity matrix according to claim 1, wherein the at least one ligand has a tree- or comb-like structure chosen from:
##STR1## ##STR2## ##STR3## ##STR4## ##STR5##

14. The polymer affinity matrix according to claim 1, wherein positive charges of at least two of the at least one functional groups are separated from each other by a distance defined by the distance between individually negatively charged groups in the binding motif of the at least one substance.

15. The polymer affinity matrix according to claim 1, wherein the at least one spacer is substantially hydrophobic or hydrophilic and has the function of an anchoring part for the at least one ligand.

16. The polymer affinity matrix according to claim 15, wherein the at least one spacer is chosen from poly- or oligoethylene glycols of the formula H--(OCH2CH2)n--OH, wherein n represents 2 to 250, polyvinylalcohols, polyvinylamines, polyolycidoles, polyethyleneimines, and polypropyleneoxides, and derivatives thereof.

17. The polymer affinity matrix according to claim 16, wherein the at least one spacer is chosen from a polyethylene glycol (PEG) in a linear and/or branched configuration and having an average molecular weight of 400 to 10,000 Daltons, and derivatives thereof.

18. The polymer affinity matrix according to claim 1, wherein the solid support is made of a material chosen from polystyrene, polyvinyl alcohols, polyhydroxystyrenes, polymers produced from chloromethylated polystyrenes or polyacrylates, polymethacrylates functionalised with hydroxy groups, hydroxyalkyl-polystyrenes, hydroxyaryl-polystyrenes, hydroxyalkyl-aryl-polystyrenes, polyhydroxyalkylated polystyrenes, polyhydroxyarylated polystyrenes, isocyanatoalkyl-polystyrenes, isocyanatoaryl-polystyrenes, carboxyalkyl-polystyrenes, carboxyaryl-polystyrenes, aminoalkyl-polystyrenes, aminoaryl-polystyrenes, polymethacrylates, cross-linked polyethyleneglycols, cellulose, silica, carbohydrates, latex, cyclo-olefine copolymers, and glass and combinations thereof.

19. The polymer affinity matrix according to claim 18, wherein the solid support has the form of a bead, gel, membrane, particle, net, woven or non-woven fabric, fibre mat, tube, film, foil or combinations thereof or

cross-linked interpenetrating networks.

20. The polymer matrix according to claim 1, wherein said polymer matrix is biocompatible and has a swelling capacity enough to allow perfusion of whole blood.

21. The polymer matrix according to claim 20, wherein the swelling capacity is about 1.5 to 20 fold from a dry state to the hydrated form.

22. The polymer affinity matrix according to claim 1, wherein said polymer matrix provides a three-dimensional complementary structure for binding the at least one substance chosen from bacteria or virus derived constituents; endotoxins; exotoxins; bacterial DNA and fragments thereof; oligonucleotides; cells; blood cells; prions; parasites; fungi; drugs after overdosing; pathogenic food additives; products from acute or chronic metabolic disturbances resulting from diabetes mellitus, liver disease, uraemia, kidney diseases or inflammation; heparin; bacteria and viruses; pathogen-**loaded** blood cells; or at least parts or degradation products thereof; DNA; phosphate; cytokines; growth factors; hormones; chemokines; uremic toxins; blood clotting proteins; procoagulatory proteins; inflammatory or proinflammatory proteins; **macrophage** migration inhibitory factor; soluble or cell surface bound proteins; soluble adhesion molecules; glucose or degradation products thereof; pyrogens; bacterial exotoxins; and products from Gram-positive bacteria.

23. The polymer affinity matrix according to any one of the claim 1, wherein said polymer matrix has a cut-off value ranging from 1x102 to 1x106 Daltons and binds hydrophobic and/or hydrophilic substances or hydrophobic and hydrophilic substances.

24. The polymer affinity matrix according to claim 1, wherein the fluid an aqueous or organic solution; a body fluid; preferably blood; therapeutical fluids; fluids for life science applications; infusion fluids or dialysis fluids in biological, diagnostic or biotechnological applications; blood products obtained from healthy donors; fluids for nutrition; and fluids for industrial use.

25. The polymer affinity matrix according to claim 1, wherein the solid support is a cross-linked polystyrene, the at least one spacer is a polyethylene glycol and the at least one each binding unit is arginine.

26. A method for removing one or more substances from a fluid and/or reducing the amount or concentration thereof comprising contacting the fluid with the polymer affinity matrix of claim 1 for a period of time sufficient to reduce the amount or concentration or remove said at least one substance.

27. The method according to claim 26, wherein the period of time ranges from 1 to 2 hours.

28. The method according to claim 26, wherein the at least one substance is an endotoxin and the fluid is blood, wherein the amount or concentration of endotoxin after being removed or reduced is below the capacity of activating components in blood or prevents activation of components or processes in blood.

29. A method for producing a polymer affinity matrix as defined in claim 1, comprising a) attaching the spacer to the solid support to obtain a first complex, and b) attaching to said first complex the ligand containing said at least one binding unit with at least one functional group; or c) attaching the spacer to the ligand containing said at

least one binding unit with at least one functional group to obtain a second complex, and d) attaching the solid support to said second complex; or e) attaching the spacer to the solid support to obtain a first complex, and f) solid phase synthesis of the ligand on the spacer bound to the solid support, or g) building up or synthesizing the spacer from monomers directly on the solid support by grafting, and h) attaching to said first complex the ligand containing said at least one binding unit with at least one functional group, or i) building up or synthesizing the spacer from monomers directly on the solid support by grafting, and k) solid phase synthesis of the ligand on the spacer bound to the solid support; wherein information about three-dimensional structure, presence of charges and hydrophobic/hydrophilic regions of the binding motif on the substance to bind is collected from X-ray crystallography, protein sequencing, protein modelling or hydrophobicity and hydrophilicity calculations and the ligand containing the binding unit is made complementary as regards charge and/or hydrophilicity/hydrophobicity to the binding motif of said substance(s).

30. The method according to claim 29 comprising the steps of, for a) and b), activation of the solid support, coupling of the spacer molecule on the solid support, synthesis of the ligand containing the binding unit, and site specific coupling of the ligand to the spacer molecule, or, for c) and d), synthesis of the ligand containing the binding unit, coupling of the spacer molecule to the ligand, activation of the solid support, and site specific coupling of the spacer-ligand complex to the solid support, or, for e) and f), activation of the solid support, coupling of the spacer molecule to the activated solid support, and solid phase synthesis of the ligand on the spacer bound to the support.

31. The method according to claim 29 comprising the steps of, for a) and b), activation of the spacer, coupling of the activated spacer to the solid support, and coupling the ligand to said activated spacer, or, for c) and d), synthesis of the ligand, activation of the spacer, site specific coupling of the ligand to the activated spacer molecule and coupling of the spacer-ligand complex to the solid support, or, for e) and f), activation of the spacer, coupling of the activated spacer to the solid support and solid synthesis of the ligand on the spacer bound to the solid support.

32. The method according to claim 26, wherein the fluid is blood or serum.

33. The method according to claim 32 wherein the method results in production of less activated blood or prevention of undesired activation of components or processes in blood.

34. The method according to claim 33, wherein the method is part of an extracorporeal blood purification process or is used in an implant in the body to contact blood or any body fluid.

35. (canceled)

36. A kit for removing one or more substances from a fluid or decreasing the amount and/or concentration thereof in said fluid comprising a polymer affinity matrix as defined in claim 1.

37. The kit according to claim 36, wherein it further comprises sample tubes, and a device for extra- and/or intracorporeal treatment of said fluid.

38. A method for producing a polymer affinity matrix for removal of one or more substances from a fluid or decreasing the amount or

concentration thereof in said fluid wherein the specific affinity of the polymer affinity matrix is dependent on any ligand applied on the polymer matrix, wherein the polymer matrix includes a solid support and at least one spacer, wherein the solid support is made of a material chosen from polystyrene, polyvinyl alcohols, polyhydroxystyrenes, polymers produced from chloromethylated polystyrenes or polyacrylates, polymethacrylates functionalised with hydroxy groups, hydroxyalkyl-polystyrenes, hydroxyaryl-polystyrenes, hydroxyalkyl-aryl-polystyrenes, polyhydroxyalkylated polystyrenes, polyhydroxyarylated polystyrenes, isocyanatoalkyl-polystyrenes, isocyanatoaryl-polystyrenes, carboxyalkyl-polystyrenes, carboxyaryl-polystyrenes, aminoalkyl-polystyrenes, aminoaryl-polystyrenes, polymethacrylates, cross-linked polyethyleneglycols, cellulose, silica, carbohydrates, latex, cyclo-olefine copolymers, and glass and combinations thereof, preferably a cross-linked polystyrene, and wherein the at least one spacer is chosen from the group consisting of poly- or oligoethylene glycols of the formula H--(OCH2CH2)n--OH, wherein n represents 2-250.

39. The method according to claim 38, wherein the solid support has the form of a bead, gel, membrane, particle, net, woven or non-woven fabric, fibre mat, tube, film, foil or combinations thereof or cross-linked interpenetrating networks.

40. The method according to claim 38, wherein the at least one spacer is chosen from a polyethylene glycol (PEG) in a linear and/or branched configuration and has an average molecular weight of 400-10 000 Daltons, and derivatives thereof.

41. The method according to claim 38, wherein the polymer matrix has a swelling capacity enough to allow perfusion of plasma or whole blood.

42. The method according to claim 41, wherein the swelling capacity is about 1.5 to 20 fold, from a dry state to the hydrated form.

43. The method according to claim 38, wherein the polymer matrix has the form of gel type beads.

44. The method according to claim 38, wherein said fluid is an aqueous or organic solutions; a body fluid; therapeutic fluids; fluids for life science applications; infusion fluids or dialysis fluids in biological, diagnostic or biotechnological application; blood products obtained from healthy donors; fluids for nutrition; and fluids for industrial use.

45. The method according to claim 38, wherein said polymer matrix has a cut-off value ranging from 1x102 to 1x106 Daltons and binds hydrophobic and hydrophilic substances or hydrophobic and/or hydrophilic substances.

46. The method according to claim 38, wherein the solid support is a cross-linked polystyrene, and the at least one spacer is a polyethylene glycol.

L26 ANSWER 9 OF 54 USPATFULL on STN
2006:143607 Hazard-free microencapsulation for structurally delicate agents, an application of stable aqueous-aqueous emulsion.
Jin, Tuo, Tianjin, CHINA
Zhu, Hua, Plainboro, NJ, UNITED STATES
Zhu, Jiahao, Brooklyn, NY, UNITED STATES
US 2006121121 A1 20060608
APPLICATION: US 2003-517122 A1 20030603 (10)

WO 2003-CN431 20030603 20060126 PCT 371 date
PRIORITY: US 2002-60384971 20020603
US 2002-10291327 20021108
US 2002-418100P 20021011 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A method for encapsulating agents into particles through stable aqueous-aqueous emulsification comprising: a. selecting polysaccharides as the dispersed phase for aqueous-aqueous emulsification, selecting aqueous polymers as the continuous phase, and selecting an stabilizing agent and its concentration for aqueous-aqueous emulsification, to provide a stable polymer aqueous-aqueous emulsion which is capable of encapsulating an agent into the polysaccharide dispersed phase; b. providing at least one agent; c. controlling the size and shape of the agent-**loaded** polysaccharide particles into appropriate size range; d. drying the emulsion; and e. removing the continuous phase after drying by washing the sample with solvent(s) which do not penetrate into the dried dispersed phase nor affect the **loaded** delicate agent(s).

2. A composition used in the method of claim 1, including an aqueous dispersed phase, an aqueous continuous phase and an aqueous surface modifier, capable to form a stable aqueous-aqueous emulsion.

3. The composition of claim 2, comprising sufficient amount of polysaccharides or derivatives thereof capable of forming the dispersed phase of the aqueous-aqueous emulsion and protecting agents encapsulated.

4. The composition of claim 3, wherein the polysaccharide is selected from the group consisting of dextran, starch, cellulose and its derivatives, and agarose and all type of poly- or oligo-sugars, which possess similar structure.

5. The composition of claim 4, wherein the average molecular weight of the polysaccharides is ranged from 2,000 to 2,000,000.

6. The composition of claim 3, wherein the agent is a biologically active agent.

7. The composition of claim 6, wherein the agent is selected from the group consisting of proteins, peptides, DNA/RNA, liposomes, and live viruses.

8. The composition of claim 7, wherein the protein or peptide is selected from the group consisting of erythropoietin (EPO), granulocyte colony stimulating factor (G-CSF), granulocyte **macrophage** colony stimulating factor (GM-CSF), interferon and β, growth hormone, calcitonin, tissue-type plasminogen activator (TPA), factor VIII, factor IX, hirudin, dornabe, and other therapeutic proteins or peptides.

9. The composition of claim 3, further comprising a small molecular sugar as complimentary agents for better protection of agents encapsulated in the polysaccharide dispersed phase during successive steps.

10. The composition of claim 9, wherein the small molecular sugar is selected from trehalose, manitol, sucrose, lactose or glycerin.

11. The composition of claim 2, comprising an aqueous polymer, which is immiscible with the polysaccharides, to form the continuous phase of the aqueous-aqueous emulsion.

12. The composition of claim 11, wherein the aqueous polymer in the continuous phase is polyethylene glycol (PEG), polyethylene oxide (PEO), polyvinyl pyrrolidone (PVP), or polyvinyl alcohol (PVA).

13. The composition of claim 12, wherein the average molecular weight of the polymer is ranged from 2,000 to 2,000,000.

14. The composition of claim 2, comprising an aqueous polymer as the surface modifier of the dispersed phase.

15. The composition of claim 14, wherein the polymeric surface modifier is selected from sodium alginate, hyaluronate, carboxymethyl cellulose, carboxymethyl dextran, dextran sulfate, and other dextran or starch devertives, or other polymers that possess negatively charged backbone and positively charged counter ions.

16. The method of claim 1, wherein the emulsion is dried through lyophilization, spray drying or a conventional drying process to solidify the agent-encapsulated polysaccharide dispersed phase.

17. Dried polysaccharide dispersed phase prepared by the method of claim 16, possessing an average diameter of 1-5 μm for inhalation and for double microencapsulation, and of 1-50 μm for other applications.

18. A method of encapsulating dried polysaccharide dispersed phase into biodegradable polymer microspheres for controlled release of bioactive agent(s) comprising: a) utilizing a solid-in-oil-in-water (S-O-W) emulsification process or a solid-in-oil-in-oil process with the dried polysaccharide dispersed phase as the solid phase; b) selecting a biodegradable polymer, dissolving the polymer in an organic solvent and suspending the dried polysaccharide dispersed phase in the polymer solution; c) selecting polymeric surfactant(s) for dispersing the solution of the biodegradable polymers in a water solution of a small molecular salt; d) the concentration of the slat solution ranges from 0.5% to 50%; e) removing the organic solvent by extraction or evaporation.

19. The method of claim 18, wherein the biodegradable polymer is PLGA, poly-pseudo CBZ-serine or other polymers.

20. Particulates of degradable polymers prepared using the method of claim 18, wherein dried polysaccharide dispersed phase is distributed in the matrix.

21. Particulates of claim 20, wherein the ratio of dried polysaccharide dispersed phase to the degradable polymer is within the range of 1:2 to 1:40.

22. A composition of any one of claims 2-15 for or acceptable for pharmaceutical applications.

L26 ANSWER 10 OF 54 USPATFULL on STN
2006:131151 Heterologus expression of trypanothione reductase from Leishmania donovani in a prokaryotic system.
Goyal, Neena, Lucknow, INDIA
Mittal, Mukul Kamar, Lucknow, INDIA
Council of Scientific and Industrial Research (non-U.S. corporation)
US 2006110791 A1 20060525
APPLICATION: US 2004-996174 A1 20041123 (10)
DOCUMENT TYPE: Utility; APPLICATION.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

CLM What is claimed is:

1. A process for heterologus expression of functionally active enzyme trypanothione reductase of Leishmania donovani strain Dd8 having accession ATCC 50212 in a prokaryotic system, said process comprising the steps of: (a) amplifying, identifying and isolating the Open Reading Frame (ORF) of trypanothione reductase having DNA SEQ ID No. I and corresponding protein SEQ ID No. 2 using forward primer having SEQ ID No. 3 and reverse primer having SEQ ID No. 4, (b) cloning of the amplified product of step (a) in cloning and expression vector, (c) subcloning of the amplified product of step (b) in cloning and expression vector, (d) transforming the cloned ORF of steps (b) (c) in a prokaryotic heterologus cloning and expression system, (e) studying the expression of the ORF transformed in step (d) under different in vitro conditions, and (f) purifying the enzyme from step (d) to homogeneity, and (g) analyzing physical and biochemical properties of the enzyme to establish the heterologus expression of soluble native form of ORF Leishmania donovani strain Dd8 having accession ATCC 50212 in a prokaryotic system.

2. A process as claimed in claim 1, wherein the enzyme trypanothione reductase, is central to thiol metabolism of the parasite and essential for the survival of the parasite in the **macrophage** system.

3. A process as claimed in claim 1, wherein the enzyme trypanothione reductase is a drug target for prevention and treatment of Leishmania donovani.

4. A process as claimed in claim 1, wherein the amplification conditions in step (a) are single cycle at 95° C. for 9 min followed by 25 cycles of 95° C. for 1-2 min., 45° C.-47° C. for 1 min. and 72° C. for 2-3 min and final single cycle of 72° C. for 4 min.

5. A process as claimed in claim 1, wherein the complete ORF in step (a) was amplified using forward oligonucelotide primer having SEQ ID No. 3 and reverse oligonucelotide primer having SEQ ID No.4.

6. A process as claimed in claim 1, wherein cloning vectors in step (b) is selected from group comprising of TOPOII, TA and pGEM-T.

7. A process as claimed in claim 6, wherein cloning vector selected is pGEM-T.

8. A process as claimed in claim 1, wherein cloning conditions in step (b) are: (a) Vector and insert ratio 1:3 (1.5 µl : 4.5 µl; 120 ng of insert DNA), (b) T4 DNA ligase 1 µl (10 U/µl), (c) 10xphosphate buffer, (d) Ligation conditions 14° C. for 18 hrs.

9. A process as claimed in claim 1, wherein expression vectors in step (c) is selected from group comprising of pQE 30, pET 21d, pET 28b, pET 41a and pGEX4T vectors.

10. A process as claimed in claim 9, wherein expression vector selected is pET41a.

11. A process as claimed in claim 1, wherein the prokaryotic cloning system in step (d) is selected from group comprising of JM 109 E.coli cells.

12. A process as claimed in claim 1, wherein the prokaryotic expression

system in step (d) are selected from group comprising of BL21 DE3 or M-15 E.coli cells.

13. A process as claimed in claim 12, wherein the expression prokaryotic system selected is BL21 DE3 E.coli cells.

14. A process as claimed in claim 1, wherein the ORF sequence (designated as LDTR or LddTRpET41aDE3) of trypanothione reductase isolated from Leishmania donovani strain Dd8 is different from other known such sequences (FIG. 4).

15. A process as claimed in claim 1, wherein the purification steps in step (f) are as following: (a) growing the E. coli cells containing LdTRORF overnight, (b) harvesting cells of step (a) and suspending them in lysis buffer, (c) sonicating the harvested cells and removing the debris from the harvested cells of step (b), (d) resuspending the cells again in phosphate buffer, (e) loading the suspended cells of step (d) in pre-equilibrated column of glutathione sepharose 4B column and incubating for about 5 hrs. at 22-20 min, (f) washing the column during incubation in step (e) twice with chilled PBS buffer, and adding thrombin at concentration of 1 U/100 µg of **loaded** protein, and (g) eluting the recombinant enzyme from step (f) by adding 20-25 ml of elution buffer.

16. A process as claimed in claim 15 wherein the E.coli cells in step (a) are grown at temperature of about 22-27° C.

17. A process as claimed in claim 15 wherein the lysis buffer in step (b) comprises of potassium phosphate buffer (10 mM) pH 7.2, 10 mM EDTA, 0.01% triton X 100, 0.1 mM PMSF

18. A process as claimed in claim 15 wherein sonication in step (c) is done 3-5 times for 30 sec to 1 min pulse with 1-2 min. cooling interval.

19. A process as claimed in claim 15 wherein the debris in step (c) is removed by centrifugation at 9000-120000 g fro 15-20 min.

20. A process as claimed in claim 15 wherein the elution buffer in step (g) is 50 mM Tris-HCl, pH 8.0.

21. A process as claimed in claim 15 wherein the recombinant protein (LdTR) isolated is having molecular mass of 54.6 kd.

22. A process as claimed in claim 15 wherein recombinant protein is having specific activity of 12.5 U/mg.

23. A process as claimed in claim 15 wherein the total yield of the recombinant protein is 16 mg/litre.

24. A process as claimed in claim 15 wherein Vmax of recombinant protein with TS_2 is 200 µM/ml/min and with $NADPH_2$ is 125 µM/ml/min.

25. A process as claimed in claim 15 wherein Km of recombinant protein with TS_2 is 50 µM and with $NADPH_2$ is 20 µM.

26. Oligonucelotide primers having SEQ ID No.3 (forward primer) and SEQ ID No.4 (Reverse primer) for isolating Open Reading Frame (ORF) of trypanothione reductase from Leishmania donovani strain Dd8 having accession ATCC 50212 and its heterologus expression in a prokaryotic system.

27. Cloning and expression vectors for isolating Open Reading Frame (ORF) of trypanothione reductase from Leishmania donovani strain Dd8 having accession ATCC 50212 and its heterologus expression in a prokaryotic system.

28. Vectors as claimed in claim 27, wherein the cloning vectors are selected from group comprising of TOPOII, TA and pGEM-T.

29. Vectors as claimed in claim 27, wherein cloning vector selected is pGEM-T.

30. Vectors as claimed in claim 27, wherein expression vectors are selected from group comprising of pQE 30, pET 21d, pET 28b, pET 41a and pGEX4T vectors.

31. Vectors as claimed in claim 30, wherein expression vector selected is pET41a.

32. A cloning prokaryotic system for isolating and cloning Open Reading Frame (ORF) of trypanothione reductase from Leishmania donovani strain Dd8 having accession ATCC 50212 and its heterologus expression in a prokaryotic system.

33. A system as claimed in claim 32, wherein the cloning vector is selected from group comprising of JM 109 E. coli cells.

34. A system as claimed in claim 32, wherein the cloning is done by using primers having SEQ ID No.3 (forward primer) and SEQ ID No.4 (Reverse primer) for Open Reading Frame (ORF) of trypanothione reductase from Leishmania donovani strain Dd8 having accession ATCC 50212

35. A system of expression prokaryotic system for expressing Open Reading Frame of trypanothione reductase from Leishmania donovani strain Dd8 having accession ATCC 50212 and its heterologus expression in a prokaryotic system

36. A system as claimed in claim 35 wherein the expression vectors are selected from group comprising of BL21 DE3 or M-15 E. coli cells.

37. A system as claimed in claim 36, wherein the expression prokaryotic system selected is BL21 DE3 E. coli cells.

38. A system as claimed in claim 35 wherein the ORF sequence (designated as LDTR or LddTRpET41 aDE3) of trypanothione reductase isolated from Leishmania donovani strain Dd8 is different from other known such sequences (FIG. 4).

L26 ANSWER 11 OF 54 USPATFULL on STN
2006:124254 YEAST-DENDRITIC CELL VACCINES AND USES THEREOF.
Duke, Richard C., Denver, CO, UNITED STATES
Bellgrau, Donald, Silverthorne, CO, UNITED STATES
Franzusoff, Alex, Denver, CO, UNITED STATES
Wilson, Cara C., Golden, CO, UNITED STATES
US 2006104986 A1 20060518
APPLICATION: US 2001-991363 A1 20011115 (9)
PRIORITY: US 2000-249173P 20001115 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1-33. (canceled)

34. An immunogenic composition, comprising: a) an isolated dendritic cell; b) a yeast vehicle selected from the group consisting of: a whole yeast, a yeast spheroplast, a yeast cytoplast, a yeast ghost, and a subcellular yeast particle; and, c) at least one immunogen that is heterologous to the yeast vehicle and that is not expressed by or **loaded** into the yeast vehicle; wherein said dendritic cell has been **loaded** intracellularly with said yeast vehicle and said at least one immunogen.

35. The immunogenic composition of claim 34, wherein said immunogen is selected from the group consisting of viral antigens, mammalian cell surface molecules, bacterial antigens, fungal antigens, protozoan antigens, helminth antigens, ectoparasite antigens, and cancer antigens.

36. The immunogenic composition of claim 34, wherein said immunogen is selected from the group consisting of: HIV-1 gag, HIV-1 env, HIV-1 pol, HIV-1 tat, HIV-1 nef, HbsAG, HbcAg, hepatitis c core antigen, HPV E6 and E7, HSV glycoprotein D, and Bacillus anthracis protective antigen.

37. The immunogenic composition of claim 34, wherein said composition comprises multiple immunogens.

38. The immunogenic composition of claim 34, wherein said composition further comprises at least one biological response modifier.

39. The immunogenic composition of claim 34, wherein said yeast vehicle is selected from the group consisting of: a whole yeast, a yeast spheroplast, a yeast cytoplast, and a yeast ghost.

40. The immunogenic composition of claim 34, wherein said yeast vehicle is selected from the group consisting of: a whole yeast and a yeast spheroplast.

41. The immunogenic composition of claim 34, wherein said yeast vehicle is a whole yeast.

42. The immunogenic composition of claim 34, wherein said yeast is a nonpathogenic yeast.

43. The immunogenic composition of claim 34, wherein said yeast is of a genus selected from the group consisting of Saccharomyces, Candida, Cryptococcus, Hansenula, Kluyveromyces, Pichia, Rhodotorula, Schizosaccharomyces and Yarrowia.

44. A method to produce an immunogenic composition, comprising loading a dendritic cell intracellularly with: a) a yeast vehicle selected from the group consisting of: a whole yeast, a yeast spheroplast, a yeast cytoplast, a yeast ghost, and a subcellular yeast particle; and, b) at least one immunogen that is heterologous to said yeast vehicle and that is not expressed by or **loaded** into the yeast vehicle.

45. The method of claim 44, wherein said step of loading a dendritic cell is accomplished by a method selected from the group consisting of: diffusion, active transport, liposome fusion, electroporation, **phagocytosis**, and bath sonication.

46. An immunogenic composition produced by the method of claim 44.

47. A method to elicit an antigen-specific humoral immune response and an antigen-specific cell-mediated immune response in a mammal, said method comprising administering to said mammal the immunogenic composition of claim 34.

48. The method of claim 47, wherein said immunogenic composition is administered by a route selected from the group consisting of: intravenous, intraperitoneal, subcutaneous, intradermal, intranodal, intramuscular, transdermal, inhaled, intranasal, oral, intraocular, intraarticular, intracranial, and intraspinal.

49. The method of claim 47, wherein said immunogenic composition is administered with a pharmaceutically acceptable excipient.

50. A method to elicit an antigen-specific humoral immune response and an antigen-specific cell-mediated immune response in a mammal, said method comprising administering to said mammal the immunogenic composition of claim 46.

L26 ANSWER 12 OF 54 USPATFULL on STN
2006:86588 Rapid generation of activated mononuclear antigen presenting cells from monocytes.
Belardelli, Filippo, Roma, ITALY
Di Pucchio, Tiziana, Roma, ITALY
Santini, Stefano Maria, Roma, ITALY
Lapenta, Caterina, Firenze, ITALY
Logozzi, Mariantonia, Roma, ITALY
Parlato, Stefania, Roma, ITALY
US 2006073589 A1 20060406
APPLICATION: US 2003-511748 A1 20030415 (10)
WO 2003-EP3922 20030415 20050906 PCT 371 date
PRIORITY: EP 2002-290994 20020419
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A cell population prepared from blood mononuclear cells, said mononuclear cells being peripheral blood mononuclear cells (PBMC) or CD14+ **monocytes**, said population containing from about 5% to about 50% of activated mononuclear antigen presenting cells (APCs) having the following characteristics: they express surface markers CD2, CD83 and CD14, MHC class I and MHC class II molecules they secrete TNF-α they are able to stimulate allogenic T lymphocytes, as shown by mixed lymphocyte reaction (MLR) measurements.

2. The cell population prepared according to claim 1, characterized in that activated mononuclear APCs are able to stimulate autologous T lymphocytes proliferation in the presence of a specific antigen.

3. Activated mononuclear APCs prepared from blood mononuclear cells and having the following characteristics: they express surface markers CD2, CD83 and CD14, MHC class I and MHC class II molecules they secrete more than 50 pg/ml of TNF-α they are able to stimulate allogenic T lymphocytes, as shown by MLR measurements.

4. Activated mononuclear APCs according to claim 3, characterized in that they express the following surface markers: CD2, CD14, CD83, CD54, CD58, CD86, MHC class I and MHC class II molecules.

5. Activated mononuclear APCs according to claim 3, characterized in that they are able to stimulate autologous T lymphocytes proliferation in the presence of a specific antigen.

6. Activated mononuclear APCs according to claim 3, characterized in that they possess **phagocytic** properties, as shown by dextran-uptake capability.

7. Activated mononuclear APCs according to claim 3, characterized in that they do not secrete detectable levels of IL-10 and secrete less than 100 pg/ml of IL-12.

8. Activated mononuclear APCs according to claim 3, said activated mononuclear APCs having been **loaded** with antigenic peptides or proteins, with a cellular extract containing at least one antigen or with nucleic acid molecules.

9. A method for preparing mononuclear Antigen Presenting Cells comprising treating said cells with ligands having receptors on the surface of blood **monocytes**, of cytokines having receptors on the surface of blood **monocytes**, of inducers of interferon synthesis by blood mononuclear cells, or of a physical stress, or a combination thereof, as means allowing the preparation from blood mononuclear cells in an appropriate medium, for about one to about five hours and preferably for less than about four hours, of a cell population according to claim 1 or of activated mononuclear APCs.

10. The method, according to claim 9, wherein said ligand is chosen among the group consisting of: cell growth factors, complement polypeptides, muramyl dipeptide analogues, natural and synthetic detoxified endotoxin derivatives, histamine, vitamin D3, arachidonic acid metabolites, aminosulfonic acid derivatives, bacillus Calmette-Guerin and bacterial membrane extracts.

11. The method according to claim 9, wherein said cytokine is type I IFN and is selected from the group consisting of: any natural IFNα, any recombinant species of IFNα, natural or recombinant IFNβ and any synthetic type I IFN.

12. The method according to claim 11, wherein said type I IFN concentration in the medium is in a range of about 100 to about 100,000 IU/ml.

13. The method according to claim 9, wherein said cytokine is chosen among the group consisting of: IFN gamma, IL-12, IL-13, IL-18, GM-CSF, TNFα and TGFβ.

14. The method according to claim 9, wherein said cytokine concentration in the medium is in a range of about 0.01 to about 10 μg/ml.

15. The method according to claim 9, wherein said medium contains type-I interferon, at a concentration of about 10,000 IU/ml, and GM-CSF, at a concentration of about 500 IU/ml.

16. The method according to claim 9, wherein said physical stress consists of one of the following events: the separation of blood mononuclear cells from the plasma contained in the blood initially containing the mononuclear cells, the exposure of the blood mononuclear cells to an osmotic change, the exposure of the blood mononuclear cells to an electrical field or the exposure of the blood mononuclear cells to a temperature variation of +/-3 to 8° C. from 37° C.

17. A process for preparing, from blood mononuclear cells, a cell population according to claim 1, or activated mononuclear APCs, comprising a step of contacting said mononuclear cells with an appropriate medium, for about one to about five hours and preferably for less than about four hours.

18. The process according to claim 17, characterized in that said medium

contains, from the initial stage of the preparation, a component selected from the group consisting of: ligands having receptors on the surface of **monocytes**, cytokines having receptors on the surface of **monocytes** and inducers of interferon synthesis by blood mononuclear cells or a combination thereof.

19. The process according to claim 18, wherein said ligand is chosen among the group consisting of: cell growth factors, complement, muramyl dipeptide analogues, natural and synthetic endotoxin derivatives, histamine, vitamin D3, arachidonic acid metabolites, aminosulfonic acid derivatives, bacillus Calmette-Guerin and bacterial membrane extracts.

20. The process according to claim 19, wherein said cytokine is type I IFN and is selected from the group consisting of: any natural IFNα, any recombinant species of IFNα, natural or recombinant IFNβ and any synthetic type I IFN.

21. The process according to claim 20, wherein said concentration of type I IFN in the medium is in a range of about 100 to about 100,000 IU/ml.

22. The process according to claim 18, wherein said cytokine is chosen among the group consisting of: IFN gamma, IL-12, IL-13, IL-18, GM-CSF, TNFα and TGFβ.

23. The process according to claim 22, wherein said concentration of cytokine in the medium is in a range of about 0.01 to about 10 µg/ml and preferably in a range of about 0.1 to about 1 µg/ml.

24. The process according to claim 23, wherein said medium contains type-I interferon, at a concentration of about 10,000 IU/ml, and GM-CSF, at a concentration of about 500 IU/ml.

25. The process for preparing, from blood mononuclear cells, a cell population according to claim 1, or activated mononuclear APCs, comprising a step of exposing said blood mononuclear cells to a physical stress, which can be: the separation of blood mononuclear cells from the plasma contained in the blood initially containg the mononuclear cells, the exposure of the cells to an osmotic change, to an electrical field or to a temperature variation of +/-3 to 8° C. from 37° C.

26. The process according to claim 18, wherein said medium also contains antigenic peptides or proteins, a cellular extract containing at least one antigen or nucleic acid molecules.

27. The process according to claim 18, wherein said process comprises: a first step of contacting mononuclear cells with an appropriate medium for about one to about five hours and preferably for less than about four hours, for the preparation of activated mononuclear APCs a second step of contacting said activated mononuclear APCs with a maturation agent.

28. Activated mononuclear APCs such as obtained by a process according to claim 17.

29. A cell population according to claim 1, or activated mononuclear APCs, wherein activated mononuclear APCs are kept under a frozen form, in an appropriate cryo-preservative solution.

30. (canceled)

31. (canceled)

32. A kit for preparing, from blood mononuclear cells, a cell population according to claim 1 or activated mononuclear APCs, in a close system allowing the exclusion of any conventional ex-vivo culture step and comprising at least: single use elements necessary for the culture and the washings of the cells, including bag(s), culture medium, buffers and connecting tube(s), including connecting tube(s) to an apheresis machine, possibly a composition comprising type I IFN and compatible additives, possibly a composition comprising a cytokine and compatible additives, possibly a composition comprising a ligand having receptors on the surface of blood **monocytes** and compatible additives, possibly a composition comprising a cell growth factor and compatible additives, possibly a composition comprising at least one antigen, or nucleic acids coding for at least one antigen, to which an immune response is of interest.

33. A pharmaceutical composition or a vaccine comprising, as active principle, activated mononuclear APCs according to claim 3, together with a pharmaceutically acceptable carrier vehicle or an auxiliary agent, in an amount of about 105 to about 1010 of said cells per dose administered.

34. A pharmaceutical composition or a vaccine containing, as an adjuvant of an active principle, activated mononuclear APCs according to claim 3, in an amount of about 105 to about 1010 of said cells per dose administered.

35. A method for treating an infectious or neoplastic disease in a patient, comprising administering an effective amount of a cell population according to claim 1 to said patient in need thereof.

36. A method for treating an infectious or neoplastic disease in a patient, comprising administering an effective amount of activated mononuclear APCs according to claim 3 to said patient in need thereof.

L26 ANSWER 13 OF 54 USPATFULL on STN
2006:60159 Pharmaceutical composition for inducing an immune response in a human or animal.
Kirkin, Alexei, Copenhagen, DENMARK
Djandjougazian, Karine, Dopenhagen, DENMARK
Zeuthen, Jesper, Hellerup, DENMARK
US 2006051324 A1 20060309
APPLICATION: US 2002-495511 A1 20021129 (10)
WO 2002-DK802 20021129 20050525 PCT 371 date
PRIORITY: PA 2001-200101770 20011129
US 2001-336706P 20011207 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A pharmaceutical composition for inducing an immune response in a human or animal, comprising dendritic cells presenting a multiplicity of cancer/testis antigens, characterized in, a) that at least five cancer/testis antigens and no lineage specific differentiation antigens or substantially no lineage specific differentiation antigens are presented by the dendritic cells, b) that the cancer/testis antigens are provided from at least one cancer cell line expressing at least five different cancer/testis antigens and no lineage specific differentiation antigens or substantially no lineage specific differentiation antigens, and c) that the dendritic cells are immature (CD1a positive, CD14 negative, and CD83 negative) during loading of the cancer/testis antigens.

2. The pharmaceutical composition according to claim 1, wherein the dendritic cells have been matured by addition of maturation factors after loading of the antigens.

3. The pharmaceutical composition according to claim 1, wherein the dendritic cells have been cultured ex vivo in growth medium without any cytokines in an initial growth phase, followed by a second growth phase in medium comprising cytokines before loading the dendritic cells with at least five cancer/testis antigens.

4. The pharmaceutical composition according to any of the preceding claims, wherein the dendritic cells are autologous dendritic cells.

5. The pharmaceutical composition according to claim 1, wherein a whole cell lysate of at least one cancer cell line expressing no lineage specific differentiation antigens or substantially no lineage specific differentiation antigens is used for loading the dendritic cells.

6. The pharmaceutical composition according to claim 1, wherein presentation of the at least five cancer/testis antigens on the dendritic cells is accomplished by whole cell fusion.

7. The pharmaceutical composition according to claim 1, wherein presentation of the at least five cancer/testis antigens is accomplished by use of exosomes.

8. The pharmaceutical composition according to any of the preceding claims, wherein the cancer cell line is a melanoma cell line and the lineage specific differentiation antigens are melanocyte differentiation antigens.

9. The pharmaceutical composition according to claim 3, wherein the melanocyte differentiation antigens comprise gp100, Melan A/Mart-1, and tyrosinase.

10. The pharmaceutical composition according to any of the claims 1-9, wherein dendritic cell precursors in the form of **monocytes** are provided from peripheral blood of the human or animal.

11. The pharmaceutical composition according to any of the claims 1-9, wherein dendritic cell precursors in the form of **monocytes** are provided from the bone marrow of the human or animal.

12. The pharmaceutical composition according to any of the claims 1-11, wherein no leukapheresis product is involved as the source of dendritic cells or **monocytes**.

13. The pharmaceutical composition according to any of the claims 1-10, wherein the dendritic cells are derived from CD14+**monocytes**.

14. The pharmaceutical composition according to claims 1-11, wherein the dendritic cells are derived from CD34+ cells.

15. The pharmaceutical composition according to any of the preceding claims, wherein the cancer/testis antigens comprise antigens selected from the MAGE-A, MAGE-B, MAGE-C, GAGE, LAGE, SSX subfamilies.

16. The pharmaceutical composition according to claim 15, wherein the cancer/testis antigens comprise antigens selected from MAGE-A1, MAGE-A2, MAGE-A3, MAGE-A4, MAGE-A5, MAGE-A6, MAGE-A8, MAGE-A9, MAGE-A10, MAGE-A11, MAGE-A12, MAGE-B1, MAGE-B2, MAGE-B3, MAGE-B4, MAGE-B5,

MAGE-B6, MAGE-B10, MAGE-B16, MAGE-B17, MAGE-C1, MAGE-C2, MAGE-C3, MAGE-C4, BAGE, GAGE-1, GAGE-2, GAGE-3, GAGE-4, GAGE-5, GAGE-6, GAGE-7, GAGE-8, NY-ESO-1, LAGE, PAGE-1, PAGE-2, PAGE-3, PAGE-4, XAGE-1, XAGE-2, XAGE-3, SSX-1, SSX-2, SSX-3, SSX-4, SSX-5.

17. The pharmaceutical composition according to any of the claims 1-14, wherein the cancer/testis antigens comprise antigens selected from SCP-1, TSP-50, TRAG-3, SAGE, IL-13R alpha, CTp11.

18. The pharmaceutical composition according to claim 16, wherein the cancer/testis antigens comprise antigens selected from MAGE-A1, MAGE-A3, MAGE-A4, MAGE-A6, MAGE-A10, MAGE-A12, and NY-ESO-1.

19. The pharmaceutical composition according to any of the preceding claims, wherein the at least five cancer/testis antigens are provided from at least two allogeneic melanoma cell lines.

20. The pharmaceutical composition according to claim 19, wherein the allogeneic melanoma cell lines are selected from DDM-1.7 (ECACC 01112339) or DDM-1.13 (ECACC 01112338).

21. The pharmaceutical composition according any of the claims 5-20, wherein the expression of the at least five cancer/testis antigens in the at least one cancer cell line is further increased before providing the whole cell lysate of said at least one cancer cell line.

22. The pharmaceutical composition according to claim 21, wherein the expression of the at least one cancer/testis antigen is increased by DNA demethylation.

23. The pharmaceutical composition according to claim 22, wherein said demethylation is provided by treatment with 5-aza-2'-deoxycytidine.

24. The pharmaceutical composition according to any of the preceding claims, wherein the cytokines are selected from the group comprising IL-4, GM-CSF, IL-13, IFN-γ, Flt-31, SCF, TNF-α.

25. The pharmaceutical composition according to claim 24, wherein the cytokines comprise IL-4 and GM-CSF.

26. The pharmaceutical composition according to any of the preceding claims, wherein the initial growth phase is from 6-48 hours, particularly from 12-34 hours, more particularly from 20-28 hours.

27. The pharmaceutical composition according to any of the claims 2-26, wherein the maturation factors comprises IL-1β, IL-6, TNF-α and PGE2.

28. A method for obtaining human or animal autologous dendritic cells **loaded** with at least five cancer/testis antigens and no lineage specific differentiation antigens or substantially no lineage specific differentiation antigens, comprising the steps: a) providing at least one cancer cell line expressing the at least five cancer/testis antigens and no lineage specific differentiation antigens or substantially no lineage specific differentiation antigens, b) providing autologous **monocytes**/dendritic cells from said human or animal, c) using a seeding density of **monocytes** between 5x106-20x106 cells per 25 cm2, d) culturing said dendritic cells ex vivo in growth medium without any cytokines in an initial growth phase, followed by a second growth phase in medium comprising cytokines, and e) loading said dendritic cells from d) with the cancer/testis antigens obtained from a whole cell lysate of the at least

one cancer cell line from a).

29. An isolated melanoma cell line, expressing at least five cancer/testis antigens and no melanocyte differentiation antigens or substantially no melanocyte differentiation antigens.

30. The isolated melanoma cell line according to claim 29, selected from the cell lines DDM-1.7 (ECACC 01112339) or DDM-1.13 (ECACC 01112338).

31. Exosomes derived from an isolated cell line according to claim 28 or 29.

32. A use of dendritic cells as antigen presenting cells in a pharmaceutical composition or a vaccine, and where the said dendritic cells are **loaded** with the antigens in their immature state at which point the dendritic cells are CD1a positive, CD14 negative, CD83 negative, wherein the dendritic cells have been cultured ex vivo in growth medium without any cytokines in an initial growth phase, followed by a second growth phase in medium comprising cytokines before loading the dendritic cell with at least five cancer/testis antigen.

33. The use according to claim 32, wherein the dendritic cells are autologous dendritic cells.

34. The use according to claim 33, wherein the autologous dendritic cells are provided from freshly drawn blood.

35. A use of a multiplicity of cancer/testis antigens obtainable from an isolated cancer cell line of claim 29 or 30 in a pharmaceutical composition or vaccine formulation.

36. The use according to claim 35, wherein the isolated cancer cell line is at least one of the cell lines of claim 30.

37. The isolated cell lines DDM-1.7 (ECACC 01112339) or DDM-1.13 (ECACC 01112338) for the preparation of a pharmaceutical composition for treatment of cancer.

38. A method for inducing an immune response in a human or animal comprising the steps: a) providing at least one cancer cell line expressing at least five cancer/testis antigens and no lineage specific differentiation antigens or substantially no lineage specific differentiation antigens, b) providing autologous dendritic cells from said human or animal, c) culturing said dendritic cells ex vivo in growth medium without any cytokines in an initial growth phase, followed by a second growth phase in fresh medium comprising cytokines, d) loading said dendritic cells from c) with the cancer/testis antigens obtained from a whole cell lysate of the at least one cancer cell line from a), and e) administering said **loaded** dendritic cells from d) to said human or animal.

39. The method according to claim 38, wherein the dendritic cells after loading with the cancer/testis antigens are matured by the addition of maturation factors such as IL-1β, IL-6, TNF-α, PGE2 before administration of the dendritic cells to said human or animal.

40. The method according to any of the claims 38-39, wherein the immune response stimulates the production of cytotoxic T-lymphocytes in the human or animal.

41. The method according to any of the claims 38-40, wherein the at least one cancer cell line is a melanoma cell line and the lineage

specific differentiation antigens are melanocyte differentiation antigens.

42. The method according to claim 41, wherein the melanocyte differentiation antigens comprise gp100, Melan A/Mart-1, and tyrosinase.

43. The method according to any of the claims 38-42, wherein the autologous dendritic cells are provided from peripheral blood of the human or animal.

44. The method according to any of the claims 38-42, wherein the autologous dendritic cells are provided from the bone marrow of the human or animal.

45. The method according to claim 43, wherein the autologous dendritic cells are derived from CD14+ **monocytes**.

46. The method according to any of the claims 43 or 44, wherein the autologous dendritic cells are derived from CD34+ cells.

47. The method according to any of the claims 38-46, wherein the cancer/testis antigens comprise antigens selected from the MAGE-A, MAGE-B, MAGE-C, GAGE, LAGE, SSX subfamilies.

48. The method according to any of the claim 38-47, wherein the cancer/testis antigens comprise antigens selected from MAGE-A1, MAGE-A2, MAGE-A3, MAGE-A4, MAGE-A5, MAGE-A6, MAGE-A8, MAGE-A9, MAGE-A10, MAGE-A11, MAGE-A12, MAGE-B1, MAGE-B2, MAGE-B3, MAGE-B4, MAGE-B5, MAGE-B6, MAGE-B10, MAGE-B16, MAGE-B17, MAGE-C1, MAGE-C2, MAGE-C3, MAGE-C4, BAGE, GAGE-1, GAGE-2, GAGE-3, GAGE-4, GAGE-5, GAGE-6, GAGE-7, GAGE-8, NY-ESO-1, LAGE, PAGE-1, PAGE-2, PAGE-3, PAGE-4, XAGE-1, XAGE-2, XAGE-3, SSX-1, SSX-2, SSX-3, SSX-4, SSX-5.

49. The method according to any of the claims 38-46, wherein the cancer/testis antigens comprise antigens selected from SCP-1, TSP-50, TRAG-3, SAGE, IL-13R alpha, CTp11.

50. The method according to claims 38-48, wherein the cancer/testis antigens comprise antigens selected from MAGE-A1, MAGE-A3, MAGE-A4, MAGE-A6, MAGE-A10, MAGE-A12, and NY-ESO-1.

51. The method according to any of the claims 38-50, wherein the expression of the at least five cancer/testis antigen in the at least one cancer cell line is further increased before lysis.

52. The method according to claim 51, wherein the expression of the at least one cancer/testis antigen is increased by DNA demethylation.

53. The method according to claim 52, wherein said demethylation is provided by treatment with 5-aza-2'-deoxycytidine.

54. The method according to any of the claims 38-53, wherein at least two allogeneic cancer cell lines are provided in step a).

55. The method according to any of the claims 38-54, wherein the allogeneic melanoma cell lines are selected from DDM-1.7 (ECACC 01112339) or DDM-1.13 (ECACC 01112338).

56. The method according to any of the claims 38-55, wherein the cytokines are selected from the group comprising IL-4, GM-CSF, IL-13, IFN-γ, Flt-31, SCF, TNF-α.

57. The method according to claim 56, wherein the cytokines comprise IL-4 and GM-CSF.

58. The method according to any of the claims 38-57, wherein the initial growth phase is from 6-48 hours, particularly from 12-34 hours, more particularly from 20-28 hours.

59. The method according to any of the claims 38-58, further comprising the step of administering to the human or animal, a substance that induces mobilization of CD14+ **monocytes** prior to step b).

60. The method according to claim 59, wherein the said substance that induces mobilization of CD14+ **monocytes** comprises G-CSF and/or GM-CSF.

61. The method according to any of the claims 38-60, further comprising the step of administering to the human or animal, a substance that induces activation of T lymphocytes after step e).

62. The method according to claim 61, wherein the said substance that induces activation of T lymphocytes comprises IL-2 or IL-12.

L26 ANSWER 14 OF 54 USPATFULL on STN
2006:40163 Novel artificial antigen presenting cells and uses therefor.
Riley, James L., Downingtown, PA, UNITED STATES
June, Carl H., Merion Station, PA, UNITED STATES
Vonderheide, Robert H., Merion Station, PA, UNITED STATES
Aqui, Nicole, Philadelphia, PA, UNITED STATES
Suhoski, Megan M., Philadelphia, PA, UNITED STATES
The Trustees of the University of Pennsylvania (U.S. corporation)
US 2006034810 A1 20060216
APPLICATION: US 2005-137807 A1 20050525 (11)
PRIORITY: US 2004-575712P 20040527 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. An isolated artificial antigen presenting cell (aAPC), said aAPC comprising a K562 cell transduced using a lentiviral vector (LV), wherein said LV comprises a nucleic acid encoding at least one immune stimulatory ligand and at least one co-stimulatory ligand and further wherein said aAPC expresses said stimulatory ligand and said co-stimulatory ligand and can stimulate and expand a T cell contacted with said aAPC.

2. The isolated aAPC of claim 1, wherein said stimulatory ligand is a polypeptide selected from the group consisting of a major histocompatibility complex Class I (MHC class I) molecule **loaded** with an antigen, an anti-CD3 antibody, an anti-CD28 antibody, and an anti-CD2 antibody.

3. The isolated aAPC of claim 1, wherein said co-stimulatory ligand is at least one co-stimulatory ligand selected from the group consisting of CD7, B7-1 (CD80), B7-2 (CD86), PD-L1, PD-L2,4-1BBL, OX40L, ICOS-L, ICAM, CD30L, CD40, CD70, CD83, HLA-G, MICA, MICB, HVEM, lymphotoxin beta receptor, ILT3, ILT4, 3/TR6, and a ligand that specifically binds with B7-H3.

4. The isolated aAPC of claim 1, wherein said co-stimulatory ligand specifically binds with at least one of a co-stimulatory molecule selected from the group consisting of CD27, CD28, 4-1BB, OX40, CD30, CD40, PD-1, ICOS, LFA-1, CD2, CD7, LIGHT, NKG2C, B7-H3, BTLA, Toll ligand receptor and a ligand that specifically binds with CD83.

5. The isolated aAPC of claim 1, wherein said co-stimulatory ligand is an antibody that specifically binds with at least one molecule selected from the group consisting of CD27, CD28, 4-1BB, OX40, CD30, CD40, PD-1, ICOS, LFA-1, CD2, CD7, LIGHT, NKG2C, B7-H3, Toll ligand receptor and a ligand that specifically binds with CD83.

6. The isolated aAPC of claim 1, wherein said aAPC further comprises Fcγ receptor selected from the group consisting of a CD32 molecule and a CD64 molecule.

7. The isolated aAPC of claim 1, wherein said LV comprises a nucleic acid encoding at least one antigen selected from the group consisting of a tumor antigen, a viral antigen, a bacterial antigen, a peptide-MHC tetramer, a peptide-MHC trimer, a peptide-MHC dimer, and a peptide-MHC monomer.

8. The isolated aAPC of claim 7, wherein said tumor antigen is selected from the group consisting of MAGE-1, MAGE-2, MAGE-3, MART-1, GP100, CEA, HER-2/Neu, PSA, WT-1, MUC-1, MUC-2, MUC-3, MUC-4, and telomerase.

9. The isolated aAPC of claim 1, wherein said LV comprises a nucleic acid encoding at least one peptide selected from a cytokine and a chemokine.

10. The isolated aAPC of claim 9, wherein said cytokine is at least one cytokine selected from the group consisting of IL-2, IL-4, IL-6, IL-7, IL-10, IL-12, IL-15, IL-21, interferon-alpha (IFNα), interferon-beta (IFNβ), interferon-gamma (IFNγ), tumor necrosis factor-alpha (TNFα), tumor necrosis factor-beta (TNFβ), granulocyte **macrophage** colony stimulating factor (GM-CSF), and granulocyte colony stimulating factor (GCSF).

11. A method for specifically inducing proliferation of a T cell expressing a known co-stimulatory molecule, said method comprising contacting said T cell with an aAPC of claim 1, further wherein said co-stimulatory ligand specifically binds with said known co-stimulatory molecule, thereby specifically inducing proliferation of said T cell.

12. A method for specifically inducing proliferation of a T cell expressing a known co-stimulatory molecule, said method comprising contacting a population of T cells comprising at least one T cell expressing said known co-stimulatory molecule with an aAPC of claim 1, wherein said aAPC expresses at least one co-stimulatory ligand that specifically binds with said known co-stimulatory molecule, wherein binding of said known co-stimulatory molecule with said co-stimulatory ligand induces proliferation of said T cell.

13. A method of specifically expanding a T cell population subset, said method comprising contacting a population of T cells comprising at least one T cell of said subset with an aAPC of claim 1, wherein said aAPC comprises at least one co-stimulatory ligand that specifically binds with a co-stimulatory molecule on said T cell of said subset, wherein binding of said co-stimulatory molecule with said co-stimulatory ligand induces proliferation of said T cell of said subset, thereby specifically expanding a T cell population subset.

14. A method of identifying a co-stimulatory ligand, or combination thereof, that specifically induces activation of a T cell subset, said method comprising contacting a population of T cells with an aAPC of claim 1, and comparing the level of proliferation of said T cell population with the level of proliferation of an otherwise identical

population of T cells not contacted with said aAPC, wherein a greater level of proliferation of said T cells contacted with said aAPC compared with the level of proliferation of said otherwise identical population of T cells not contacted with said aAPC, is an indication that said co-stimulatory ligand specifically induces activation of said T cell.

15. A method for inducing a T cell response to an antigen in a mammal, said method comprising administering to said mammal the aAPC of claim 1, wherein said aAPC further comprises an MHC Class I molecule **loaded** with said antigen, wherein said aAPC induces proliferation of a T cell specific for said antigen, thereby inducing a T cell response to said antigen in said mammal.

16. A method of inducing a T cell response to an antigen in a mammal in need thereof, said method comprising obtaining a population of cells from said mammal wherein said population comprises T cells, contacting said population of cells with an aAPC of claim 1, wherein said aAPC further comprises an MHC Class I complex **loaded** with said antigen, whereby contacting said cells with said aAPC induces proliferation of an antigen-specific T cell specific for said antigen, isolating said antigen-specific T cell from said population of cells, and administering said antigen-specific T cells to said mammal, thereby inducing a T cell response to said antigen in said mammal.

17. A method of specifically expanding a population of T regulatory (Treg) cells, the method comprising contacting said population with an aAPC of claim 1, wherein said aAPC further comprises an Fcγ receptor **loaded** with an anti-CD3 antibody and an anti-CD28 antibody, the method further comprising contacting said population of cells with a cytokine, wherein binding of said anti-CD3 antibody and said anti-CD28 antibody with said Treg cells induces proliferation of said Treg cells, thereby specifically expanding a population of Treg cells.

18. The method of claim 17, wherein said cytokine is interleukin-2.

19. A kit for specifically inducing proliferation of a T cell expressing a known co-stimulatory molecule, said kit comprising an effective amount of an aAPC, wherein said aAPC comprises a K562 cell transduced using a lentiviral vector (LV), wherein said LV comprises a nucleic acid encoding at least one co-stimulatory ligand that specifically binds said known co-stimulatory molecule, wherein binding of said known co-stimulatory molecule with said co-stimulatory ligand stimulates and expands said T cell, said kit further comprising an applicator and an instructional material for the use of said kit.

20. A kit for specifically inducing proliferation of a T cell expressing a known stimulatory molecule, said kit comprising an effective amount of an aAPC, wherein said aAPC comprises a K562 cell transduced using a lentiviral vector (LV) wherein said LV comprises a nucleic acid encoding at least one stimulatory ligand that specifically binds said known stimulatory molecule, wherein binding of said known stimulatory molecule with said stimulatory ligand stimulates and expands said T cell, said kit further comprising an applicator and an instructional material for the use of said kit.

21. A kit for specifically expanding a T cell population subset, said kit comprising an effective amount of an aAPC, wherein said aAPC comprises a K562 cell transduced using a lentiviral vector (LV), wherein said LV comprises a nucleic acid encoding at least one co-stimulatory ligand that specifically binds a co-stimulatory molecule on said T cell population, wherein binding of said co-stimulatory molecule with said co-stimulatory ligand stimulates and expands said T cell population,

said kit further comprising an applicator and an instructional material for the use of said kit.

22. A kit for identifying a co-stimulatory ligand, or combination of said ligands, that specifically induces activation of a T cell subset, said kit comprising a plurality of aAPCs wherein each said aAPC comprises a K562 cell transduced using a lentiviral vector (LV), wherein said LV comprises a nucleic acid encoding at least one known co-stimulatory ligand that specifically binds with a co-stimulatory molecule, said kit further comprising an applicator and an instructional material for the use of said kit.

L26 ANSWER 15 OF 54 USPATFULL on STN
2005:318852 Method for treating a patient undergoing chemotherapy.
Rodgers, Kathleen, Long Beach, CA, UNITED STATES
DiZerega, Gere, Los Angeles, CA, UNITED STATES
University of Southern California (U.S. corporation)
US 2005277595 A1 20051215
APPLICATION: US 2004-842877 A1 20040510 (10)
PRIORITY: US 2000-201470P 20000503 (60)
US 2000-220804P 20000725 (60)
US 2000-233375P 20000918 (60)
US 2000-235040P 20000925 (60)
US 2000-243955P 20001027 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. An improved method for chemotherapy in a human patient, wherein the improvement comprises administering to the human chemotherapy patient an amount effective for treating or preventing chemotherapy side effects of at least one active agent comprising a sequence of at least three contiguous amino acids of groups R1-R8 in the sequence of general formula I R1--R2--R3--R4--R5--R6--R7--R8 wherein R1 is selected from the group consisting of H, Asp, Glu, Asn, Acpc (1-aminocyclopentane carboxylic acid), Ala, Me2Gly, Pro, Bet, Glu(NH2), Gly, Asp(NH2) and Suc, R2 is selected from the group consisting of Arg, Lys, Ala, Om, Ser(Ac), Sar, D-Arg and D-Lys; R3 is selected from the group consisting of Val, Ala, Leu, Lys, norLeu, Ile, Gly, Pro, Aib, Acpc and Tyr; R4 is selected from the group consisting of Tyr, Tyr(PO3)2, Thr, Ser, Ala, homoSer and azaTyr; R5 is selected from the group consisting of Ile, Ala, Leu, norLeu, Val and Gly; R6 is selected from the group consisting of His, Arg or 6-NH2-Phe; R7 is selected from the group consisting of Pro or Ala; and R8 is selected from the group consisting of Phe, Phe(Br), Ile and Tyr, excluding sequences including R4 as a terminal Tyr group; and wherein the active agent is not SEQ ID NO: 1.

2. The method of claim 1 wherein the active agent comprises a sequence of at least four contiguous amino acids of groups R1-R8 in the sequence of general formula I.

3. The method of claim 1 wherein the active agent comprises a sequence of at least five contiguous amino acids of groups R1-R8 in the sequence of general formula I.

4. The method of claim 1 wherein the active agent comprises a sequence of at least six contiguous amino acids of groups R1-R8 in the sequence of general formula I.

5. The method of claim 1 wherein the active agent comprises a sequence

of at least seven contiguous amino acids of groups R1-R8 in the sequence of general formula I.

6-10. (canceled)

11. The method of claim 1 wherein the active agent comprises a sequence selected from the group consisting of angiotensinogen, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO: 32, SEQ ID NO:33, SEQ ID NO: 34; SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, and SEQ ID NO:42.

12-14. (canceled)

15. The method of claim 1 wherein the active agent comprises a sequence of the following general formula II: Asp-Arg-R1-R2-Ile-His-Pro-R3, wherein R1 is selected from the group consisting of Val, Pro, Lys, Norleu, and Leu; R2 is selected from the group consisting of Ala, Tyr, and Tyr(PO3)2; and R3 is Phe or is absent.

16-18. (canceled)

19. The method of claim 1 wherein the side effect is selected from the group consisting of hematopoietic toxicity, decreased mobilization of hematopoietic progenitor cells from bone marrow into the peripheral blood; anemia, myelosuppression, pancytopenia, thrombocytopenia, neutropenia, lymphopenia, leukopenia, stomatitis, alopecia, headache, and muscle pain.

20. The method of claim 1 wherein the active agent is administered at a dosage of between about 2.5 µg/kg/day and about 100 µg/kg/day.

21. The method of claim 1 wherein the active agent is administered at a dosage of between about 10 µg/kg/day and about 75 µg/kg/day.

22. The method of claim 1 wherein the active agent is administered parenterally.

23. The method of claim 22 wherein the active agent is administered subcutaneously or intravenously.

24. The method of claim 23 wherein the active agent is self-administered.

25. The method of claim 24 wherein the active agent is administered into the abdomen or thigh.

26. The method of claim 1 wherein administration of the active agent is initiated either at the time chemotherapy is initiated, or subsequently to initiation of chemotherapy.

27. The method of claim 1 wherein the active agent is administered once per day.

28. A pharmaceutical composition comprising a) an amount of the active agent of claim 1 sufficient to provide a dosage to a patient of between about 2.5 µg/kg/day and about 100 µg/kg/day; and b) a pharmaceutically acceptable carrier.

29. The pharmaceutical composition of claim 28 wherein the active agent is selected from the group consisting of SEQ ID NO:4 and SEQ ID NO:41

30. (canceled)

31. The pharmaceutical composition of claim 30 wherein the cytokine is selected from the group consisting of granulocyte colony stimulating factor, granulocyte-**macrophage**-CSF, epidermal growth factor, interleukin 11, thrombopoietin, megakaryocyte development and growth factor, pixykines, stem cell factor, FLT-ligand, and interleukins 1, 3, 6, and 7.

32. (canceled)

33. An article of manufacture, comprising the pharmaceutical composition of claim 28 **loaded** in a drug delivery device.

34. (canceled)

L26 ANSWER 16 OF 54 USPATFULL on STN
2005:280562 Immunotherapy compositions, method of making and method of use thereof.
Higbee, Russell G., Orlando, FL, UNITED STATES
Barber, Glen N., Miami, FL, UNITED STATES
Kachurin, Anatoly M., Orlando, FL, UNITED STATES
Kachurina, Olga M., Orlando, FL, UNITED STATES
Gappa-Fahlekamp, Heather, Oviedo, FL, UNITED STATES
Warren, William L., Orlando, FL, UNITED STATES
Balachandran, Siddharth, Miami, FL, UNITED STATES
Thomas, Emmanuel, Miami, FL, UNITED STATES
Parkhill, Robert, Orlando, FL, UNITED STATES
US 2005244505 A1 20051103
APPLICATION: US 2004-8936 A1 20041213 (11)
PRIORITY: US 2003-528613P 20031211 (60)
US 2004-605554P 20040831 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A composition for modulating innate immune system in a mammal, said composition comprising a microparticle comprising a polycationic polymer; a modulator of FADD-dependent pathway; and a modulator of TLR pathway, wherein said modulator of FADD-dependent pathway and said modulator of TLR pathway are associated with said microparticle, and wherein said microparticle is capable of being **phagocytosed** by an antigen presenting cell.

2. The composition of claim 1, wherein said modulator of FADD-dependent pathway is selected from the group consisting of dsRNA, poly(IC), a component of the FADD-dependent pathway, a DNA plasmid encoding a component of the FADD-dependent pathway, a bacterium, and a fungus.

3. The composition of claim 2, wherein the FADD-dependent pathway modulator is a dsRNA encoding FADD.

4. The composition of claim 2, wherein the FADD-dependent pathway modulator is a dsRNA representing a silencing RNAi capable of suppressing the FADD-dependent pathway.

5. The composition of claim 4, wherein the silencing RNAi suppresses FADD expression.

6. The composition of claim 1, wherein said modulator of TLR pathway is selected from the group consisting of dsRNA, poly (IC), a synthetic mimetic of viral dsRNA, and a ligand for TLR, a bacterium, and a fungus.

7. The composition of claim 1, wherein said modulator of FADD-dependent pathway and modulator of TLR-dependent pathway are the same dsRNA molecule.

8. The composition of claim 1, wherein said microparticle is further coated with a targeting molecule that binds specifically to an antigen presenting cell.

9. The composition of claim 8, wherein said targeting molecule is an antibody.

10. The composition of claim 9, wherein said targeting molecule is heat shock protein gp96.

11. The composition of claim 1, further comprising a poly(lactide-co-glycolide)(PLGA) matrix containing a cytokine or an antigen, wherein said microparticle is encapsulated in said matrix.

12. The composition of claim 1, further comprising a cytokine encapsulated in said microparticle.

13. The composition of claim 12, wherein said cytokine is selected from the group consisting of IL-12, IL-1α, IL-1β, IL-15, IL-18, IFNα, IFNβ, IFNγ, IL-4, IL-10, IL-6, IL-17, IL-16, TNFα, and MIF.

14. The composition of claim 13, wherein said microparticle further comprising one or more hydrophobic polymers so that a desired release rate of cytokine is achieved.

15. The composition of claim 14, wherein said one or more hydrophobic polymers comprise PLGA, poly(caprolactone) or poly(oxybutirate).

16. The composition of claim 13, wherein said microparticle ftirther comprising an amphiphilic polymer.

17. The composition of claim 16, wherein said amphiphilic polymer is poly(ethylene imine) (PEI).

18. The composition of claim 1, wherein said composition further comprising a tumor antigen or a DNA encoding a tumor antigen, and wherein said tumor antigen or DNA encoding a tumor antigen is associated with said microparticle.

19. The composition of claim 1, wherein said microparticle has a diameter in the range of about 0.5 μm to about 20 μm.

20. The composition of claim 1, wherein said polycationic polymer is chitosan.

21. The composition of claim 1, further comprising a pharmaceutically acceptable carrier.

22. A composition for modulating immune system in a mammal, comprising **phagocytosable** chitosan microparticles **loaded** with a nucleic acid and a protein.

23. The composition of claim 22, wherein said nucleic acid is a dsRNA, poly (IC), a synthetic mimetic of viral dsRNA, or DNA molecule.

24. The composition of claim 22, wherein said protein is a cytokine.

25. The composition of claim 24, wherein said cytokine is selected from the group consisting of IL-12, IL-1α, IL-1β, IL-15, IL-18, IFNα, IFNβ, IFNγ, IL-4, IL-10, IL-6, IL-17, IL-16, TNFα, and MIF.

26. The composition of claim 22, wherein said protein is an antibody that binds an antigen presenting cell.

27. The composition of claim 22, wherein said nucleic acid is a dsRNA and said protein is a TLR ligand.

28. The composition of claim 22, wherein said nucleic acid is a dsRNA and said protein is FADD.

29. The composition of claim 22, wherein said chitosan particle further comprises a hydrophobic polymer.

30. The composition of claim 29, wherein said hydrophobic polymer is selected from the group consisting of PLGA, poly(caprolactone) and poly(oxybutirate).

31. The composition of claim 22, wherein said chitosan particle further comprises PEI.

32. The composition of claim 22, further comprising a pharmaceutically acceptable carrier.

33. A method for treating viral, bacterial or fungal infection in a mammal, comprising administering to said subject an effective amount of the composition of claim 22.

34. The method of claim 33, wherein said viral infection is caused by human immunodeficiency virus (HIV), influenza virus (INV), encephalomyocarditis virus (EMCV), stomatitis virus (VSV), parainfluenza virus, rhinovirus, hepatitis A virus, hepatitis B virus, hepatitis C virus, apthovirus, coxsackievirus, Rubella virus, rotavirus, Denque virus, yellow fever virus, Japanese encephalitis virus, infectious bronchitis virus, Porcine transmissible gastroenteric virus, respiratory syncytial virus, papillomavirus, Herpes simplex virus, varicellovirus, Cytomegalovirus, variolavirus, Vacciniavirus, suipoxvirus or coronavirus.

35. The method of claim 34, wherein said viral infection is caused by HIV, INV, EMCV, or VSV.

36. A method for treating cancer in a mammal, comprising administering to said subject an effective amount of the composition of claim 22.

37. The method of claim 36, wherein said cancer is breast cancer, colon-rectal cancer, lung cancer, prostate cancer, skin cancer, osteocarcinoma, or liver cancer.

38. A composition for modulating immune response in a mammal, said composition comprising: a microparticle comprising a polycationic polymer; a dsRNA or poly (IC) as an innate immune response booster; and an antigen, wherein said dsRNA or poly (IC) and said antigen are associated with said microparticle and wherein said microparticle is

capable of being **phagocytosed** by an antigen presenting cell.

39. The composition of claim 38, further comprising a cytokine, wherein said cytokine is associated with said microparticle.

40. The composition of claim 39, wherein said cytokine is selected from the group consisting of IL-12, IL-1α, IL-1β, IL-15, IL-18, IFNα, IFNβ, IFNγ, IL-4, IL-10, IL-6, IL-17, IL-16, TNFα, and MIF.

41. The composition of claim 38, further comprising a heatshock protein, wherein said heatshock protein is associated with said microparticle.

42. The composition of claim 38, wherein said dsRNA or poly (IC) and said antigen are associated with said microparticle through surface attachment, encapsulation, or a combination of surface attachment and encapsulation.

43. The composition of claim 38, wherein said immune response is innate immune response.

44. The composition of claim 38, wherein said immune response is adaptive immune response.

45. A composition for modulating innate immune response in a mammal, said composition comprising: a microparticle comprising a polycationic polymer; an immune activator capable of inducing the formation of an innateosome complex regulating TBK-1/IKK-δ-mediated activation of IRF3, and a modulator of TLR pathway, wherein said activator for an innateosome complex and said modulator of TLR pathway are associated with said microparticle and wherein said microparticle is capable of being **phagocytosed** by an antigen presenting cell.

46. The composition of 45, wherein said immune activator is a dsRNA.

47. The composition of 46, wherein said dsRNA is a viral dsRNA.

48. A method for preparing a multifunctional microparticle for immune modulation of a mammal, comprising: (a) fabricating chitosan microparticles by precipitation, gelation and spray (b) incubating the chitosan microparticles in a solution comprising a nucleic acid, a protein, or both.

49. The method of claim 48, following step (b), further comprising the steps of: (c) washing the chitosan microparticles after incubation; and (d) drying the washed chitosan microparticles.

50. The method of claim 48, wherein said nuclei acid is selected from the group consisting of dsRNA, poly (IC), synthetic mimetic of viral dsRNA, and DNA, wherein said protein is selected from the group consisting of antibodies, cytokines, TLR ligand, gp96, and tumor antigens.

51. The method of claim 50, wherein said cytokine is selected from the group consisting of IL-12, IL-1α, IL-1β, IL-15, IL-18, IFNα, IFNβ, IFNγ, IL-4, IL-10, IL-6, IL-17, IL-16, TNFα, and MIF.

52. The method of claim 48, further comprising: admixing chitosan with a nucleic acid, a protein, or both before fabricating the chitosan microparticles by precipitation, gelation, and spray.

53. A method for identifying anti-viral genes relating to FADD signaling pathway, comprising: treating FADD-deficient cells and corresponding wild-type cells with poly (IC); isolating RNAs from poly (IC)-treated FADD-deficient cells and poly (IC)-treated wild-type cells; hybridizing the isolated RNAs to a gene array; and identifying genes that are differentially expressed in poly (IC)-treated FADD-deficient cells comparing to poly (IC)-treated wild-type cells.

L26 ANSWER 17 OF 54 USPATFULL on STN
2005:260871 Methods and compositions comprising bacteriophage nanoparticles.
Rao, Venigalla Basaveswara, Silver Spring, MD, UNITED STATES
US 2005226892 A1 20051013
APPLICATION: US 2004-15294 A1 20041217 (11)
PRIORITY: US 2003-530527P 20031217 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. An immunogenic composition comprising: a) a Hoc and/or Soc fusion protein, b) a Hoc and/or Soc negative T4 bacteriophage particle; wherein the Hoc and/or Soc fusion protein is **loaded** onto the Hoc and/or Soc negative T4 bacteriophage particle in vitro.

2. The composition of claim 1, wherein the fusion protein comprises Hoc and/or Soc bound to a protein comprising interleukins, lipid A, phospholipase A2, endotoxins, staphylococcal enterotoxin B and other toxins, Type I Interferon, Type II Interferon, Tumor Necrosis Factor (TNF-α or b), Transforming Growth Factor-β ("TGF-β"), Lymphotoxin, Migration Inhibition Factor, Granulocyte-**Macrophage** Colony-Stimulating Factor ("CSF"), **Monocyte-Macrophage** CSF, Granulocyte CSF, vascular epithelial growth factor ("VEGF"), Angiogenin, transforming growth factor ("TGF-α"), heat shock proteins, carbohydrate moieties of blood groups, Rh factors, fibroblast growth factor, and other inflammatory and immune regulatory proteins, nucleotides, DNA, RNA, mRNA, sense, antisense, cancer cell specific antigens; such as MART, MAGE, BAGE, and heat shock proteins (HSPs); mutant p53; tyrosinase; mucines, such as Muc-1, PSA, TSH, autoimmune antigens; immunotherapy drugs, such as AZT; and angiogenic and anti-angiogenic drugs, such as angiostatin, endostatin, and basic fibroblast growth factor, and vascular endothelial growth factor (VEGF), prostate specific antigen and thyroid stimulating hormone, or fragments thereof.

3. The composition of claim 1, wherein the composition is effective for treating bacterial disease, fungal disease, rickettsial disease, chlamydial disease, viral disease parasitic infection, sexually transmitted diseases, sarcoidosis, and prion disease.

4. The composition of claim 1, further comprising a pharmaceutical carrier.

5. A method for making a vaccine, comprising: a) constructing a Hoc and/or Soc fusion protein, b) isolating a Hoc and/or Soc negative T4 bacteriophage particle, and c) loading the Hoc and/or Soc fusion protein onto the T4 bacteriophage particle in vitro.

6. The method of claim 5, wherein the loading the Hoc and/or Soc fusion protein onto the T4 bacteriophage particle comprises incubation of the Hoc and/or Soc fusion protein with the T4 bacteriophage particle in a reaction buffer.

7. The method of claim 5, wherein the reaction buffer comprises Tris

buffered saline, phosphate buffered saline, hepes buffer.

8. The method of claim 5, wherein the fusion protein comprises a foreign protein fused to a Hoc or Soc protein or fragment thereof.

9. The method of claim 8, wherein the foreign protein is antigenic.

10. The method of claim 9, wherein the foreign protein comprises comprising interleukins, lipid A, phospholipase A2, endotoxins, staphylococcal enterotoxin B and other toxins, Type I Interferon, Type II Interferon, Tumor Necrosis Factor (TNF-α or b), Transforming Growth Factor-β ("TGF-β"), Lymphotoxin, Migration Inhibition Factor, Granulocyte-**Macrophage** Colony-Stimulating Factor ("CSF"), **Monocyte-Macrophage** CSF, Granulocyte CSF, vascular epithelial growth factor ("VEGF"), Angiogenin, transforming growth factor ("TGF-α"), heat shock proteins, carbohydrate moieties of blood groups, Rh factors, fibroblast growth factor, and other inflammatory and immune regulatory proteins, nucleotides, DNA, RNA, mRNA, sense, antisense, cancer cell specific antigens; such as MART, MAGE, BAGE, and heat shock proteins (HSPs); mutant p53; tyrosinase; mucines, such as Muc-1, PSA, TSH, autoimmune antigens; immunotherapy drugs, such as AZT; and angiogenic and anti-angiogenic drugs, such as angiostatin, endostatin, and basic fibroblast growth factor, and vascular endothelial growth factor (VEGF), prostate specific antigen and thyroid stimulating hormone, or fragments thereof or a fragment thereof.

11. The method of claim 5, wherein the vaccine is a multi-component vaccine.

12. The method of claim 5, wherein the T4 bacteriophage particle is devoid of DNA.

13. The method of claim 5, wherein the T4 bacteriophage particle comprises a DNA construct.

14. A method for assembling a multi-protein complex on the surface of a T4 bacteriophage particle, comprising: a) constructing a first Hoc and/or Soc fusion protein having a first foreign protein, or an active fragment thereof, b) constructing a second Hoc and/or Soc fusion protein having a second foreign protein, or an active fragment thereof, c) isolating a Hoc and/or Soc negative T4 bacteriophage particle, and d) loading the first Hoc and/or Soc fusion protein and the second Hoc and/or Soc fusion protein onto Hoc and/or Soc negative T4 bacteriophage particle in vitro.

15. The method of claim 14, wherein the first foreign protein domain is antigenic.

16. The method of claim 14, wherein the second foreign protein domain is antigenic.

17. The method of claim 14, wherein the loading of the first Hoc and/or Soc fusion protein and the second Hoc and/or Soc fusion protein onto the Hoc and/or Soc negative T4 bacteriophage particle facilitates an interaction between the first foreign protein domain and the second foreign protein domain.

18. The method of claim 17, wherein the interaction between first foreign protein domain and the second foreign protein domain facilitates the presentation of an antibody binding site.

19. The method of claim 14, wherein the first protein comprises a

mycobacterial antigen and wherein the second protein comprises a human immunodeficiency viral antigen.

20. The method of claim 14, wherein the first or second protein comprises comprising interleukins, lipid A, phospholipase A2, endotoxins, staphylococcal enterotoxin B and other toxins, Type I Interferon, Type II Interferon, Tumor Necrosis Factor (TNF-α or b), Transforming Growth Factor-β ("TGF-β"), Lymphotoxin, Migration Inhibition Factor, Granulocyte-**Macrophage** Colony-Stimulating Factor ("CSF"), **Monocyte-Macrophage** CSF, Granulocyte CSF, vascular epithelial growth factor ("VEGF"), Angiogenin, transforming growth factor ("TGF-α"), heat shock proteins, carbohydrate moieties of blood groups, Rh factors, fibroblast growth factor, and other inflammatory and immune regulatory proteins, nucleotides, DNA, RNA, mRNA, sense, antisense, cancer cell specific antigens; such as MART, MAGE, BAGE, and heat shock proteins (HSPs); mutant p53; tyrosinase; mucines, such as Muc-1, PSA, TSH, autoimmune antigens; immunotherapy drugs, such as AZT; and angiogenic and anti-angiogenic drugs, such as angiostatin, endostatin, and basic fibroblast growth factor, and vascular endothelial growth factor (VEGF), prostate specific antigen and thyroid stimulating hormone, or fragments thereof.

L26 ANSWER 18 OF 54 USPATFULL on STN
2005:240626 Elicitation of antibodies to self peptides in mice by immunization with dendritic cells.
Bowdish, Katherine S., Del Mar, CA, UNITED STATES
Kretz-Rommel, Anke, San Diego, CA, UNITED STATES
US 2005208627 A1 20050922
APPLICATION: US 2004-16382 A1 20041217 (11)
PRIORITY: US 2003-503738P 20030918 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A method of producing an antibody comprising the steps of: a) isolating dendritic cells from a host animal; b) incubating the dendritic cells with a cell-derived material including a self peptide of interest to form an immunogen; c) immunizing the host animal with the immunogen; d) harvesting cells that produce antibodies to the self peptide of interest; and e) recovering one or more antibodies from the harvested cells.

2. A method as in claim 1 wherein the cell-derived material is a cell lysate.

3. A method as in claim 1 wherein the cell-derived material is a plasma membrane.

4. A method of producing an antibody comprising the steps of: f) isolating dendritic cells from a host animal; g) incubating the dendritic cells with a self peptide of interest to form an immunogen; h) isolating B cells from a second animal of a different species than the host animal; i) incubating the B cells with a peptide from the second animal homologous to the self peptide of interest to form a **loaded** B cell; j) immunizing the host animal with the immunogen and the **loaded** B cell; k) harvesting cells that produce antibodies to the self peptide of interest; and l) recovering one or more antibodies from the harvested cells.

5. A method as in claim 4 wherein the step of isolating dendritic cells from a host animal comprises utilizing a rodent as the host animal.

6. A method as in claim 4 wherein the step of isolating B cells from a second animal of a different species than the host animal comprises utilizing a human as the second animal.

7. A method as in claim 4 wherein the step of isolating dendritic cells comprises selecting dendritic cells utilizing antibodies to markers associated with dendritic cells selected from the group consisting of cell surface molecules responsible for T cell activation, adhesion molecules and costimulatory molecules.

8. A method as in claim 4 wherein the step of isolating dendritic cells comprises selecting dendritic cells utilizing antibodies to markers for dendritic cells selected from the group consisting of CD54 and CD11.

9. A method as in claim 4 wherein the dendritic cells are incubated with a self peptide of interest obtained from cell lysate of the host animal.

10. A method as in claim 4 wherein the dendritic cells are incubated with a self peptide of interest obtained from a plasma membrane.

11. A method as in claim 4 wherein the self peptide of interest is coated onto a polystyrene bead.

12. A method as in claim 4 wherein the step of immunizing the host animal with the immunogen immunizing the host animal with the immunogen and the **loaded** B cell further comprises the step of adding an adjuvant to the immunogen and the **loaded** B cell.

13. A method as in claim 12 wherein the step of adding an adjuvant comprises selecting an adjuvant from the group consisting of IL-1, IL-2, IL-4, IL-5, IL-6, IL-7, IL-10, IL-12, IL-15, granulocyte-**macrophage** colony stimulating factor, granulocyte colony stimulating factor, interferon-γ, TNF-α, TGF-β, Flt-3, and CD40 ligand.

14. A method as in claim 12 wherein the step of adding an adjuvant comprises utilizing a CpG oligonucleotide as the adjuvant.

15. A method as in claim 4 wherein said step of harvesting cells comprises removing cells comprising antibodies from the host, isolating RNA from the removed cells, constructing an antibody library and identifying one or more antibodies that bind to the self peptide of interest.

16. An antibody produced in accordance with the method of claim 1.

17. An antibody produced in accordance with the method of claim 4.

18. A fusion molecule comprising an antibody to DC-Specific ICAM-3 grabbing non-integrin linked to a self peptide of interest.

19. A fusion molecule according to claim 18 wherein the antibody is chemically linked to the self peptide of interest.

20. A fusion molecule according to claim 18 wherein the antibody is genetically linked to the self peptide of interest.

L26 ANSWER 19 OF 54 USPATFULL on STN
2005:199904 Tangential flow filtration devices and methods for leukocyte enrichment.
Bosch, Marnix L, Medina, WA, UNITED STATES
Harris, Paul C., Bothell, WA, UNITED STATES

Monahan, Steven J., Kenmore, WA, UNITED STATES
Turner, Allen, Seattle, WA, UNITED STATES
Boynton, Alton L., Redmond, WA, UNITED STATES
Lodge, Patricia A., Everett, WA, UNITED STATES
Northwest Biotherapeutics, Inc., Bothell, WA, UNITED STATES, 98021 (U.S. corporation)
US 2005173315 A1 20050811
APPLICATION: US 2003-517871 A1 20030619 (10)
WO 2003-US19428 20030619
PRIORITY: US 2002-390730P 20020619 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A tangential flow filtration device for preparing a cell population enriched for leukocytes, comprising: a remover unit having a cross-flow chamber, a filtrate chamber and a filter disposed therebetween, the filter in fluid communication with the cross-flow chamber and the filtrate chamber; the cross-flow chamber having an inlet and an outlet, the inlet disposed to introduce a sample of blood constituents comprising leukocytes into the cross-flow chamber and parallel to the surface of the filter; and the outlet centrally disposed in a portion of the cross-flow chamber opposite the filter surface; the filter having an average pore size ranging from about 1 to about 10 microns; such that flow of the sample across the filter enriches the sample of blood constituents for leukocytes.

2. The device according to claim 1, further comprising: a means for providing a predetermined input rate of the sample to the inlet of the cross-flow chamber; a means for controlling a filtration rate of filtrate through the filter and into the filtrate chamber; and wherein the filtration rate controlling means limits the filtration rate to less than the unopposed filtration rate for the filter.

3. The device according to claim 1 or claim 2, wherein the filter pore size is about 3 microns to about 7 microns.

4. The device according to claim 1 or claim 2, wherein the filter pore size is about 3 microns to about 5.5 microns.

5. The device according to claim 1 or claim 2, further comprising: a source of blood constituents in fluid communication with the cross-flow chamber inlet.

6. The device according to claim 5, wherein the source of blood constituents is a leukopheresis device.

7. The device according to claim 1 or claim 2, further comprising: a recovery unit comprising an inlet and an outlet, the cross-flow chamber and the recovery unit interconnected in loop format, wherein the cross-flow chamber inlet is in fluid communication with the recovery unit outlet, and the cross-flow chamber outlet is in fluid communication with the recovery unit inlet.

8. The device according to claim 7, wherein the recovery unit further comprises a sample inlet and a wash inlet.

9. The device according to claim 8, further comprising a source of replacement liquid in fluid communication with the wash inlet.

10. The device according to claim 9, wherein the replacement liquid is an isotonic buffer or tissue culture media.

11. The device according to claim 1 or claim 2, wherein the cross-flow chamber is cylindrical and the outlet is located opposite the center of the filter and perpendicular to a surface of the filter.

12. The device according to claim 1 or claim 2, further comprising a cell-processing apparatus in fluid communication with the remover unit.

13. The device according to claim 12, wherein the cell processing apparatus comprises beads.

14. The device according to claim 12, wherein the cell processing apparatus comprises a means for culturing the cell population enriched for leukocytes.

15. The device according to claim 14, wherein the means for culturing comprises: a vessel having a first port and a second port; a monocytic dendritic cell precursor adhering substrate, the substrate in fluid communication with the first port and the second port; a screen for retaining the substrate within the vessel, the screen having a pore size sufficient to allow passage of monocytic dendritic cell precursors and dendritic cells therethrough; a drain line in fluid communication with the first port; and a collection line in fluid communication with the first port.

16. The device according to claim 15, further comprising a plurality of fluid sources in fluid communication with the first port or the second port.

17. The device according to claim 15, further comprising a sealable tissue culture vessel adapted to aseptically receive the monocytic dendritic cell precursors.

18. The device according to claim 17, wherein the sealable tissue culture vessel is a tissue culture bag, flask or bioreactor.

19. The device according to claim 15, wherein the fluid sources comprise binding media, washing buffer and elution buffer.

20. The device according to claim 15, further comprising a pump in fluid communication with the plurality of fluid sources and the first port.

21. The device according to claim 15, further comprising: a temperature control means to maintain the substrate at a predetermined temperature.

22. The device according to claim 21, wherein the temperature controlling means is a heater.

23. A tangential flow device for enriching a sample of blood constituents for leukocytes, comprising: a remover unit comprising a cross-flow chamber (3) and a filtrate chamber (4) separated by a filter (5), wherein the cross-flow chamber (3) has an inlet (6) and an outlet (7), the outlet centrally disposed in an upper portion of the chamber, and wherein the inlet is disposed above the filter and introduces fluid into the cross-flow chamber substantially parallel to the filter; a means for providing a predetermined input rate (14) of the sample through the cross-flow chamber inlet; and a means for reducing a filtration rate (15) through the filter; wherein the filter has a pore size of about 3 microns to about 7 microns; and whereby the sample is enriched for leukocytes in a retentate in the cross-flow chamber.

24. A tangential flow device for enriching a sample comprising blood constituents for leukocytes, comprising: a remover unit (1) having a

cross-flow chamber (3) and a filtrate chamber (4) separated by a filter (5), the cross-flow chamber having an inlet (6) and an outlet (7), the outlet disposed above the inlet and centrally disposed in an upper portion of the chamber, and wherein the filter is disposed below and substantially parallel to the cross-flow chamber inlet; means for providing a predetermined input rate (14) of the sample through the cross-flow chamber inlet; means for providing a predetermined filtration rate (15) of the fluid through the filter, wherein the predetermined filtration rate is about one-fifth to about one one-hundredth of the predetermined input rate; and means for providing a predetermined concentration of blood cells in the sample, wherein the predetermined concentration of blood cells is about 107 to about 1010 cells per milliliter; wherein the filter has pores having a pore size of about 3 microns to about 7 microns; and whereby the sample is enriched for leukocytes in a retentate in the cross-flow chamber.

25. A method for separating leukocytes from a sample of blood constituents from a subject wherein the sample comprises leukocytes, the method comprising: (1) introducing the sample into a remover unit through an inlet in the remover unit; (2) subjecting the sample to cross-flow substantially parallel to a filter having a pore size of about 1 to about 10 microns; (3) subjecting the fluid to filtration through the filter; and (4) selectively removing non-leukocyte blood constituents from the sample to form a cell population enriched for leukocytes.

26. The method according to claim 25, further comprising: preparing the sample from the subject by leukopheresis, density centrifugation, differential lysis, filtration, or preparation of a buffy coat, for introduction in the remover unit.

27. The method according to claim 25, wherein the non-leukocyte blood constituents include plasma and platelets.

28. The method according to claim 25, wherein the non-leukocyte blood constituents include erythrocytes.

29. The method according to claim 25, wherein the leukocytes comprise **monocytes**.

30. The method according to claim 25, further comprising repeating steps (1), (2), and (3) at least two times to form cell population enriched for leukocytes.

31. The method according to claim 25, wherein the enriched cell population comprises at least about 20% leukocytes.

32. The method according to claim 25, wherein the enriched cell population comprises at least about 60% leukocytes.

33. The method according to claim 25, further comprising inducing a vortex motion of the sample in the cross-flow chamber.

34. The method according to claim 25, further comprising washing the cell population enriched for leukocytes with a wash solution.

35. The method according to claim 25, further comprising preparing monocytic dendritic cell precursors from the cell population enriched for leukocytes.

36. The method according to claim 35, wherein the isolation of monocytic dendritic cell precursors comprises: contacting a monocytic dendritic

cell precursor adhering substrate with the cell population enriched for leukocytes; allowing monocytic dendritic cell precursors in the cell population to reversibly adhere to the substrate to form complexes comprising monocytic dendritic cell precursors and substrate; separating the complexes from the non-adhering leukocytes to obtain complexes comprising monocytic dendritic cell precursors; and culturing the monocytic dendritic cell precursors to differentiate the precursors to form immature or mature dendritic cells.

37. The method according to claim 36, wherein the monocytic dendritic cell precursors are eluted from the substrate prior to culturing.

38. The method according to claim 36, wherein the monocytic dendritic cell precursors are cultured on the substrate.

39. The method according to claim 36, wherein the substrate comprises glass, polystyrene, plastic or glass-coated polystyrene microbeads.

40. A method for enriching a sample of blood constituents for leukocytes, comprising: (1) introducing the sample into a tangential flow filtration (TFF) unit, the TFF unit comprising a cross-flow chamber, a filtrate chamber, and a filter in fluid communication with the cross-flow chamber and the filtrate chamber, the filter having a pore size of about 1 to about 10 microns; (2) recirculating the sample through the TFF unit at a predetermined input rate and a predetermined filtration rate, the predetermined input rate at least five times the predetermined filtration rate; wherein the predetermined filtration rate is less than the unopposed filtration rate for the filter; and (3) isolating a cell population enriched for leukocytes.

41. The method according to claim 40, wherein the enriched cell population is substantially free of non-leukocyte blood constituents.

42. The method according to claim 40, further comprising: collecting blood from a subject and preparing the sample from the blood by leukopheresis, density centrifugation, differential lysis, filtration, or preparation of a buffy coat.

43. The method according to claim 40, wherein the non-leukocyte blood constituents include plasma and platelets.

44. The method according to claim 41, wherein the non-leukocyte blood constituents include erythrocytes.

45. The method according to claim 40, wherein the leukocytes comprise **monocytes**.

46. The method according to claim 40, wherein the enriched cell population comprises at least about 20% leukocytes.

47. The method according to claim 40, wherein the enriched cell population comprises at least about 60% leukocytes.

48. The method according to claim 40, wherein the sample flows in a vortex motion in the cross-flow chamber.

49. The method according to claim 40, further comprising washing the enriched cell population with a wash solution.

50. The method according to claim 40, further comprising preparing dendritic cells from the enriched cell population.

51. The method according to claim 50, wherein the dendritic cells are prepared by: contacting a monocytic dendritic cell precursor adhering substrate with the enriched cell population; allowing monocytic dendritic cell precursors in the enriched cell population to reversibly adhere to the substrate to form complexes comprising monocytic dendritic cell precursors and substrate; separating the complexes from the non-adhering leukocytes to obtain complexes comprising monocytic dendritic cell precursors; and culturing the monocytic dendritic cell precursors to differentiate the precursors to form immature or mature dendritic cells.

52. The method according to claim 51, wherein the substrate comprises glass, polystyrene, plastic or glass-coated polystyrene microbeads.

53. The method according to claim 51, further comprising isolating the immature or mature dendritic cells.

54. The method according to claim 45, wherein the **monocytes** are cultured with cytolines that promote the differentiation of **monocytes** into dendritic cells.

55. The method according to claim 54, wherein the cytokines are GM-CSF, GM-CSF and IL-4.

56. The method according to claim 54, wherein the dendritic cells are matured to mature dendritic cells.

57. The method according to claim 54, wherein the dendritic cells are cultured with an antigen under conditions conducive for processing the antigen to form antigen **loaded** dendritic cells.

58. The method according to claim 57, further comprising the step of administering the antigen **loaded** dendritic cells to an individual.

59. The method according to claim 57, wherein the antigen **loaded** dendritic cells are cultured with a maturation agent to mature the cells into mature antigen presenting dendritic cells.

60. The method according to claim 40, wherein the filter has a pore size of about 3 to about 5.5 microns.

61. The method according to claim 60, wherein the leukocytes comprise CD34+ cells.

62. The method according to claim 61, wherein the sample of blood constituents is from a donor tat has been treated with at least one stem cell mobilizing agent.

63. The method according to claim 62, wherein the stem cell mobilizing agent is G-CSF or cyclophosphamide.

64. The method according to claim 61, further comprising enriching the leukocytes for the CD34+ cells.

65. The method according to claim 64, wherein the enrichment of leukocytes for the CD34+ cells comprises using an anti-CD34 antibody conjugated to magnetic beads.

66. The method according to claim 61, further comprising expanding the CD34+ cells ex vivo.

67. The method according to claim 60, further comprising preparing

monocyte-derived pluripotent stem cells from the cell population enriched for leukocytes.

68. The method according to claim 60, further comprising inducing differentiation of a progenitor or stem cell.

69. The method according to claim 60, further comprising inducing transdifferentiation of a differentiated cell.

L26 ANSWER 20 OF 54 USPATFULL on STN
2005:130682 Compositions and methods for treatment of neoplastic disease.
Terman, David S., Pebble Beach, CA, UNITED STATES
US 2005112141 A1 20050526
APPLICATION: US 2004-937758 A1 20040908 (10)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A mammalian cell comprising an exogenous nucleic acid encoding a superantigen which is expressed in said cell which cell also produces or expresses all α-anomers of monoglycosylceramide or diglycosylceramide, wherein expression of said superantigen and said mono- or di-glycosylceramide is capable of eliciting an effective anti-tumor immune response in a mammal into which said cell is introduced.

2. The cell of claim 1 which is selected from a group consisting of (a) a tumor cell (b) an accessory cell (c) a tumor cell/accessory cell hybrid

3. The cell of claim 1 wherein said mammal bears a tumor, against which the antitumor response is directed, said tumor being selected from the group consisting of a carcinoma, a melanoma, a sarcoma, a neuroblastoma, an astrocytoma, a lymphoma and a leukemia.

4. The cell of claim 1 wherein the superantigen is selected from the group consisting of a Staphylococcal enterotoxin and a Streptococcal pyrogenic exotoxin.

5. A method of treating a tumor or neoplastic disease in a subject, comprising administering to said subject an effective amount of the cells of any of claims 1-4, wherein said nucleic acid is introduced in vivo into a cell that produces or expresses said mono- or diglycosylceramide.

6. A method of treating a tumor or neoplastic disease in a subject comprising administering an effective amount of the cells of any of claims 1-4 wherein said superantigen exogenous nucleic acids is introduced ex vivo or in vitro into a cell which produces or expresses said mono- or di-glycosylceramide.

7. A composition useful for treating a tumor or neoplastic disease in a subject comprising a conjugate or complex of (a) a superantigen; and (b) a glycosylceramide.

8. The composition of claim 7 wherein the glycosylceramide is selected from a group consisting of (a) an α-1-4-galabiosylceramide, (b) an α-1-4-globotriosylceramide, (c) an α-1-4-globoteterasylceramide or (d) a glycosylphosphatidylinositol-anchored α-1-4-galabiosylceramide, (e) a glycosylphosphatidylinositol-anchored α-1-4-globotriosylceramide, and (f) a glycosylphosphatidylinositol-anchored α-1-4-

globoteterasylceramide.

9. The composition of claim 7, wherein the glycosylceramide comprises a phytosphingosine chain having unsubstituted hydroxyl groups at its C3- and C4 position.

10. The composition of claim 7, wherein the length of the ceramide fatty acyl chain is from about 12 to about 24 carbons.

11. The composition of claim 7, wherein the sphingosine portion of the ceramide has a chain length of about 10 to about 13 carbons.

12. The composition of claim 7, wherein the conjugate or complex further comprises CD1 receptors, MHC class I molecules, MHC class II molecules or superantigen receptors.

13. The composition of claim 7-12 wherein the superantigen-glycosylceramide is in or on a vesicle, exosome, liposome, phage display, prokaryotic cell surface or eukaryotic cell surface.

14. The composition of claims 7-12 wherein said complex or conjugate is obtained by shedding from cells expressing said complexes or conjugates.

15. The composition of claim 7-12 wherein the superantigen-glycosylceramide conjugate, or, if present, said superantigen-GPI-glycosylceramide conjugate, is chemically linked by a crosslinking agent

16. The compositions of claims 13 wherein the superantigen-glycosylceramide is **loaded** onto a prokaryotic or eukaryotic cell surface.

17. A method of treating a tumor or neoplastic disease in a subject comprising administering to the subject an effective amount of cells **loaded** with the compositions of any of claims 7-12, so that the cells present the composition to the immune system, thereby inducing an anti-tumor immune response.

18. A method of treating a tumor or neoplastic disease in a subject comprising administering to the subject an effective amount of compositions of claim 13, thereby inducing an anti-tumor immune response.

19. A method of treating a tumor or neoplastic disease in a subject comprising administering to the subject an effective amount of the composition of claim 15, thereby inducing an anti-tumor immune response.

20. The method of claim 17 wherein the composition is a superantigen-glycosylceramide-CD1 conjugate or complex wherein the glycosylceramide is selected from a group consisting of (a) an α1-4-galabiosylceramide, (b) an α-1-4-globotriosylceramide, (c) an α-1-4-globoteterasylceramide or (d) a glycosylphosphatidylinositol-anchored α-1-4-galabiosylceramide, (e) a glycosylphosphatidylinositol-anchored α-1-4-globotriosylceramide, and (f) a glycosylphosphatidylinositol-anchored α-1-4-globoteterasylceramide.

21. The method of claim 18 wherein the composition is a superantigen-glycosylceramide-CD1 conjugate or complex wherein the glycosylceramide is selected from a group consisting of (a) an α1-4-galabiosylceramide, (b) an α-1-4-globotriosylceramide, (c) an α-1-4-globoteterasylceramide or (d) a glycosylphosphatidylinositol-anchored α-1-4-galabiosylceramide,

(e) a glycosylphosphatidylinositol-anchored α-1-4-globotriosylceramide, and (f) a glycosylphosphatidylinositol-anchored α-1-4-globoteterasylceramide.

22. The method of claim 17 wherein the cells are selected from the group consisting of: (a) dendritic cells; (b) **macrophages** or **monocytes**; (c) fibroblasts; (d) keratinocytes; (e) stromal cells; (f) antigen presenting cell; (g) tumor cells; (h) lymphocytes; and (i) a combination of any two or more of (a)-(h).

23. The method of claim 18 wherein the cells are selected from the group consisting of: (a) dendritic cells; (b) **macrophages** or **monocytes**; (c) fibroblasts; (d) keratinocytes; (e) stromal cells; (f) antigen presenting cell; (g) tumor cells; (h) lymphocytes; and (i) a combination of any two or more of (a)-(h).

24. The method of claim 19 wherein the cells are selected from the group consisting of: (a) dendritic cells; (b) **macrophages** or **monocytes**; (c) fibroblasts; (d) keratinocytes; (e) stromal cells; (f) antigen presenting cell; (g) tumor cells; (h) lymphocytes; and (i) a combination of any two or more of (a)-(h).

25. The method of claim 20 wherein the cells are selected from the group consisting of: (a) dendritic cells; (b) **macrophages** or **monocytes**; (c) fibroblasts; (d) keratinocytes; (e) stromal cells; (f) antigen presenting cell; (g) tumor cells; (h) lymphocytes; and (i) a combination of any two or more of (a)-(h).

26. The compositions of claim 7-12, wherein the superantigen is selected from the group consisting of a Staphylococcal enterotoxin and a Streptococcal pyrogenic exotoxin.

27. A method of treating a tumor or neoplastic disease in a subject comprising administering to said subject an effective amount of the composition of any of claims.

28. A method of preparing a population of immunotherapeutically active T or NKT cells useful to treat a tumor or neoplastic disease in a subject, comprising: (a) providing to (i) a subject in vivo or (ii) a population of T and/or NKT cells ex vivo or in vitro the cells of any of claims 1-4 or a composition of any of claims 7-12 to prime or stimulate the production of a population of tumor-specific T cells and/or NKT cells, (b) obtaining said primed or stimulated T or NKT cells; (c) optionally, further contacting said primed or stimulated T or NKT cells with any of said cells or compositions ex vivo to expand and further stimulate said T or NKT cells. thereby preparing said of immunotherapeutically active cells.

29. A method of treating a tumor or neoplastic disease in a subject, comprising administering an effective amount of T and/or NKT cells prepared in accordance with claim 24 to said subject to treat said tumor or neoplastic disease.

30. A composition useful for treating a tumor or neoplastic disease in a subject comprising naked DNA encoding a superantigen conjugated to a protein which induces apoptosis of tumor cells in said subject.

31. The composition of claim 25 wherein the protein is selected from a group consisting of (a) Fas; (b) Perforin; (c) Granzyme B; (d) Tumor Necrosis Factor α or .quadrature.; (e) Verotoxin; and (f) a Verotoxin A chain, B chain or hybrid AB chain.

32. A composition useful for treating a tumor or neoplastic disease in a subject comprising naked DNA encoding a superantigen conjugated to a verotoxin.

33. A composition useful for treating a tumor or neoplastic disease in a subject comprising naked DNA encoding a superantigen conjugated to a protein or peptide that has at least about 30% sequence identity to the Gal(α1-4)Gal-binding region of a verotoxin.

34. A composition useful for treating a tumor or neoplastic disease in a subject comprising naked DNA encoding a superantigen conjugated to a protein or peptide that has at least about 45% sequence identity to the Gal(α1-4)Gal-binding region of a verotoxin.

35. The composition of claim 33 or 34 wherein the peptide or protein has the amino acid sequence of all or part of any Gal(α1-4)Gal-binding portion of: (a) the 63 kDa extracellular peptide of the interferon α receptor; or (b) the N terminal extracellular domain of CD19.

36. An apoptotic cell preparation or lysate useful for treating a tumor or neoplastic disease in a subject, comprising a cell population that has been (a) transfected with naked DNA encoding a superantigen; and (b) treated to undergo apoptosis or lysis.

37. A cell which has ingested or been transfected with the apoptotic preparation or lysate of claim 36, thereby rendering the cell effective in presenting material expressed from transfecting nucleic acid or material ingested to the immune system of a mammal to elicit an anti-tumor immune response.

38. A method for treating a tumor or neoplastic disease in a subject, comprising (a) providing to a population of cells selected from the group consisting of: (i) tumor cells; (ii) accessory cells; (iii) tumor cell/accessory cell hybrids; (iv) cells with an inherent or acquired -galactosidase deficiency; and (v) a combination of any two or more of (i)-(iv), said apoptotic cell preparation or said lysate of claim 36, to produce an immunostimulatory cell population; (b) administering to said subjected an amount of said immunostimulatory cell population effective to treat said tumor or neoplastic disease.

39. The method of claim 38 wherein said accessory cells are dendritic cells and said hybrid cells (iii) are dendritic cell/tumor cell hybrids.

40. The method of claim 38 wherein the providing step (a) is in vivo.

41. The method of claim 38 wherein the providing step (a) is in vitro.

42. A method of treating a tumor or neoplastic disease in a subject comprising administering to said subject an effective amount of cells according to claim 36, wherein said ingested lysate, transfecting nucleic acid or other apoptotic matter is presented to the immune system to elicit a tumoricidal response.

43. A composition useful for treating a tumor or neoplastic disease in a subject comprising a lipoprotein which is capable of binding to receptors in tumor microvasculature and eliciting apoptosis of tumor endothelial cells and eliciting an effective anti-tumor response in a mammal into which said lipoprotein is introduced.

44. The composition of claim 43 wherein the lipoprotein is selected from the group consisting of: (a) low density lipoproteins (a) chylomicrons (b) very low density lipoproteins (c) apolipoproteins (d) oxidized low

density lipoproteins (e) oxidized low density lipoprotein byproducts (f) oxidized low density lipoproteins mimics (g) low density lipoprotein complexed with compounds which enhance or promote the uptake by cells expressing LDL or oxidized LDL receptors.

45. The composition of claim 44 wherein the compounds which enhance or promote the uptake by cells expressing LDL or oxidized LDL receptors are selected from a group consisting of: (a) fibronectin (b) collagen (c) heparan

46. A composition useful for treating a tumor or neoplastic disease in a subject comprising a conjugate or complex of: (a) a superantigen; and (b) a lipoprotein

47. The composition of claim 46 wherein the lipoprotein is selected from the group consisting of: (a) low density lipoproteins (a) chylomicrons (b) very low density lipoproteins (c) apolipoproteins (d) oxidized low density lipoproteins (e) oxidized low density lipoprotein byproducts (f) oxidized low density lipoproteins mimics (g) low density lipoprotein complexed with compounds which enhance or promote the uptake by cells expressing LDL or oxidized LDL receptors.

48. the composition of claim 47 wherein the compounds which enhance or promote the uptake by cells expressing LDL or oxidized LDL receptors are selected from a group consisting of: (a) fibronectin (b) collagen (c) heparan

49. The compositions of claims 46-48 wherein the superantigen-lipoprotein conjugate is in or on a vesicle, exosome, liposome, phage display, prokaryotic cell surface or eukaryotic cell surface.

50. The compositions of claim 49 which are are derived from a group consisting of: (a) a mammalian cell transfected with superantigen genes (b) a sickle cell or sickle cell precursor transfected with superantigen genes (c) a yeast cell or mutant transfected with superantigen genes (d) a Staphylococcus carnosus transfected with superantigen genes. (e) a Sphingomonas paucimobilis transfected with superantigen genes

51 The compositions of claims 46-50 wherein the superantigen is selected from the group consisting of a Staphylococcal enterotoxin and a Streptococcal pyrogenic exotoxin.

52. The method of treating a tumor or neoplastic disease in a subject comprising administering to the subject an effective amount of the compositions of claims 46-50 so that the composition localizes in tumor microvasuclature and is presented to the immune system, thereby inducing an anti-tumor response

53. A mammalian cell useful for treating a tumor or neoplastic disease in a subject comprising a nucleic acid encoding a receptor for LDL or oxidized LDL which renders the said cell capable of binding LDL or oxyLDL and undergoing apoptosis and eliciting an effective anti-tumor response.

54. The mammalian cell of claim 53 comprising a second exogenous nucleic acid encoding a superantigen such that the expression of said superantigen and products of the first nucleic acid alone or in combination are capable of eliciting an effective anti-tumor immune response.

55. The cell of claim 53 is selected from a group consisting of: (a) tumor cells (b) endothelial cells (c) stromal cells

56. The cell of claim 53 wherein the LDL or oxidized LDL receptor is selected for the group consisting of: (a) scavenger receptors expresssed on endothelial cells and **macrophages** (b) LOX-1 receptor (c) oxidized low density lipoprotein receptor (d) CD36 receptor (e) Acetyl low density lipoprotein receptor (f) low density lipoprotein receptor (g) low density lipoprotein receptor-related protein (LRP)

57. The cell of claim 55 wherein the superantigen is selected from the group consisting of a Staphylococcal enterotoxin and a Streptococcal pyrogenic exotoxin.

58. A method of treating a tumor or neoplastic disease in a subject comprising administering an effective amount of exogenous LDL receptor, oxyLDL receptor nucleic acid or superantigen nucleic acid wherein they are introduced into the cell in vivo.

59. A composition useful for treating a tumor or neoplastic disease in a subject comprising a conjugate or complex of: (a) a superantigen; and (b) a LDL or oxidized low density lipoprotein receptor

60. The composition of claim 59 wherein the LDL or oxidized LDL receptor is selected for the group consisting of: (a) scavenger receptors expresssed on endothelial cells and **macrophages** (b) LOX-1 receptor (c) oxidized low density lipoprotein receptor (d) CD36 receptor (e) Acetyl low density lipoprotein receptor (f) low density lipoprotein receptor (g) low density lipoprotein receptor-related protein (LRP) (h) apolipoprotein receptors

61. The compositions of claims 58-59 wherein the LDL and oxidized LDL receptors are in the form of naked DNA.

62. The compositions of claims 59-60 wherein the LDL receptor or superantigen or LDL receptor is a polypeptide or nucleic acid in or on a vesicle, exosome, liposome, phage display, plasmid, expression vector, prokaryotic cell surface or eukaryotic cell surface.

63. The vesicles, exosomes prokaryotic and eukaryotic cell surfaces of claim 61 which are derived from a group consisting of: (a) a mammalian cell transfected with superantigen genes (b) a sickle cell or sickle cell precursor transfected with superantigen genes (c) a yeast cell or mutant yeast cell transfected with superantigen genes (d) a Staphylococcus carnosus transfected with superantigen genes. (e) a Sphingomonas paucimobilis transfected with superantigen genes

64. The compositions of claims 58-63 wherein the superantigen is selected from the group comprising a Staphylococcal enterotoxin and Streptococcal pyrogenic exotoxin

65. A mammalian cell comprising an exogenous nucleic acid encoding a superantigen which is expressed in said cell which cell also produces or expresses low density lipoproteins, wherein expression of said superantigen and said native LDL or oxidized LDL or biologically active LDL mimics and byproducts is capable of eliciting an effective anti-tumor immune response in a mammal into which said cell is introduced.

66. The cell of claim 65 which is selected from a group consisting of (a) a tumor cell (b) a endothelial cell (b) a sickled cell or sickled cell precursor

67. The cell of claim 65 wherein the the low density lipoproteins are

selected from the group consisting of: (a) native low density lipoprotein (a) oxidized low density lipoprotein (b) low density lipoprotein mimics (c) low density lipoprotein byproducts

68. The cell of claim 65 wherein said mammal bears a tumor, against which the antitumor response is directed, said tumor being selected from the group consisting of a carcinoma, a melanoma, a sarcoma, a neuroblastoma, an astrocytoma, a lymphoma and a leukemia.

69. A method of treating a tumor or neoplastic disease in a subject, comprising administering to said subject an effective amount of the cells of any of claims.

70. A method of treating a tumor or neoplastic disease in a subject comprising administering an effective amount of the cells of any of claims 65-67 wherein said superantigen exogenous nucleic acids is introduced ex vivo or in vitro into a cell which produces or expresses low density lipoproteins

71. A method of treating a tumor or neoplastic disease in a subject comprising administering an effective amount of the cells of any of claims 65-67 wherein said superantigen exogenous nucleic acids and apolipoprotein nucleic acid is introduced ex vivo or in vitro into a cell which thereby expresses superantigen and apolipoprotein.

72. The method of claim 70-71 wherin the low density lipoproteins are selected from a group consisting of: (a) native low density lipoprotein (a) oxidized low density lipoprotein (b) low density lipoprotein mimics (c) low density lipoprotein byproducts

73. A mammalian cell comprising expressing a α-monogalactosylceramide or α-digalactosylceramide or oxidized low density lipoprotein individually or in any combination which is (are) capable of binding to tumor microvasculature, inducing apoptosis and eliciting an effective anti-tumor immune response in a mammal into which said cell is introduced.

74. The cell of claim 73 which also expresses a superantigen

75. The cell of claims 73-74 which is selected from a group consisting of: (a) a tumor cell (b) a sickled cell or sickled cell precursor

76. A mammalian tumor cell/accessory cell hybrid cell comprising an exogenous nucleic acid encoding a superantigen which is expressed in said cell such that expression of said superantigen renders the said cell capable of elicting an effective anti-tumor immune response in a mammal into which said cell is introduced.

77. The cell of claim 76 wherein said hybrid cell is a dendritic cell/tumor cell hybrid.

78. The cells of claims 73-77 wherein said mammal bears a tumor, against which the antitumor response is directed, selected from the group consisting of a carcinoma, a melanoma, a sarcoma, a neuroblastoma, a lymphoma and a leukemia.

79. The cell of claim 73-77 wherein the superantigen is selected from the group consisting of a Staphylococcal enterotoxin and a Streptococcal pyrogenic exotoxin.

80. A method of treating a tumor or neoplastic disease in a subject comprising administering an effective amount of nucleic acids in vivo to

the tumor/accessory tumor/accessory cell hybrid cells of claims 76-77.

81. A method of treating a tumor or neoplastic disease in a subject comprising administering an effective amount of the cells of claim 76-77 wherein said exogenous nucleic acids are introduced into the cell ex vivo or in vitro.

L26 ANSWER 21 OF 54 USPATFULL on STN
2005:104602 Delivery of biologically active agents.
Kelly, Rodney William, Edinburgh, UNITED KINGDOM
Calder, Andrew Alexander, Edinburgh, UNITED KINGDOM
US 2005089535 A1 20050428
APPLICATION: US 2003-470984 A1 20020211 (10)
WO 2002-GB557 20020211
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A method of delivering a biologically active agent to the cervix, the method comprising using a needleless injector.

2. A method according to claim 1 wherein the needleless injector is a liquid injector.

3. A method according to claim 1 wherein the needless injector is a powder injector.

4. A method according to claim 1 wherein the biologically active agent is a cervical ripening agent.

5. A method according to claim 4 wherein the cervical ripening agent is any one or more of a prostaglandin, MCP-1 and IL-8.

6. A method according to claim 1 wherein the biologically active agent is a vasodilator or precursor thereof, a chemokine or a cytokine which stimulates **monocyte** or granulocyte entry into cervical tissue.

7. A method of ripening the female cervix, the method comprising administering a cervical ripening agent to the cervix using a needleless injector.

8. A system for delivering a biologically active agent to the cervix comprising an agent which is biologically active on the cervix and a needleless injector.

9. A system according to claim 8 wherein the biologically active agent is a cervical ripening agent.

10. A system according to claim 8 wherein the needleless injector is a liquid injector.

11. A system according to claim 8 wherein the needleless injector is a powder injector.

12. A needleless injector **loaded** for injection with an agent which is biologically active on the cervix.

13. A needleless injector according to claim 12 wherein the biologically active agent is a cervical ripening agent.

14. A needleless injector according to claim 12 which is a liquid injector.

15. A needleless injector according to claim 12 which is a powder injector.

16. A vial for insertion into, and containing an agent for delivery by, a needleless injector wherein the agent is an agent which is biologically active on the cervix.

17. A vial according to claim 16 wherein the agent is a cervical ripening agent.

18. A method of preparing a needleless injector for use in delivering a biologically active agent to the cervix, the method comprising loading the injector with the biologically active agent.

19. A method according to claim 18 wherein the agent is **loaded** in a vial disposed for insertion into the needleless injector.

20. A pharmaceutical formulation comprising an agent for delivery to the cervix and a carrier suitable for use in a needleless injector.

21. A pharmaceutical formulation according to claim 20 wherein the formulation contains particles of a density between about 0.1 and about 25 g/cm3 and of a size between 0.1 and 250 μm which particles comprise the said agent.

22. A pharmaceutical formulation according to claim 20 comprising an agent which permeabilises a mucosal surface, such as dimethylsulphoxide.

23. Use of a cervical ripening agent in the manufacture of a medicament for treating a female in need of a cervical ripening agent wherein the cervical ripening agent is for delivery using a needleless injector.

24-26. (canceled).

L26 ANSWER 22 OF 54 USPATFULL on STN
2005:99050 Methods for inducing the differentiation of blood monocytes into functional dendritic cells.
Edelson, Richard L., Westport, CT, UNITED STATES
Berger, Carole L., Bronx, NY, UNITED STATES
US 2005084966 A1 20050421
APPLICATION: US 2004-884356 A1 20040701 (10)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A method for inducing the differentiation of **monocytes** in an extracorporeal quantity of a subject's blood into dendritic cells comprising the steps of: (a) obtaining an extracorporeal quantity of a subject's blood; (b) loading the extracorporeal quantity of blood in a plastic container; (c) subjecting the container to physical perturbation for a sufficient time to induce differentiation of **monocytes** into functional dendritic cells; and (d) incubating the extracorporeal quantity of blood following physical perturbation for a sufficient time to allow differentiation of the **monocytes** to a dendritic cell phenotype.

2. The method of claim 1, wherein the physical perturbation of the blood is continued for a period of between about 15 minutes to about 3 hours at a temperature between about 10 degrees Centigrade to about 50 degrees Centigrade.

3. The method of claim 2, further comprising the step of selecting or isolating dendritic cells from the treated blood based on the presence of a substantially dendritic cell-specific polynucleotide, polypeptide or both.

4. The method of claim 3, further comprising the step of administering back to said donor the dendritic cell to improve the donor's immunological state.

5. The method of claim 1, wherein the container is a plastic tube, and the step of subjecting the container to physical perturbation is performed in a tube rotator.

6. A method for inducing the differentiation of **monocytes** in an extracorporeal quantity of a subject's blood into dendritic cells comprising the steps of: (a) obtaining an extracorporeal quantity of a subject's blood; (b) subjecting the extracorporeal quantity of blood to leukapheresis to obtain a white blood cell concentrate; (c) loading the white blood cell concentrate in a plastic container; (c) subjecting the container to physical perturbation for a sufficient time to induce differentiation of **monocytes** into functional dendritic cells;about; and (d) incubating the blood following physical perturbation for a sufficient time to allow differentiation of the **monocytes** to a dendritic cell phenotype.

7. The method of claim 6, wherein the physical perturbation of the blood is continued for a period of between about 15 minutes to about 3 hours at a temperature between about 10 degrees Centigrade to about 50 degrees Centigrade.

8. The method of claim 7, further comprising the step of selecting or isolating dendritic cells from the treated blood based on the presence of a substantially dendritic cell-specific polynucleotide, polypeptide or both.

9. The method of claim 8, further comprising the step of administering back to said donor the dendritic cell to improve the donor's immunological state.

10. The method of claim 7, wherein the container is a plastic tube, and the step of subjecting the container to physical perturbation is performed in a tube rotator.

11. A method for inducing the differentiation of **monocytes** in an extracorporeal quantity of a subject's blood into dendritic cells comprising the steps of: (a) obtaining an extracorporeal quantity of a subject's blood; (b) passing the blood through a packed column, wherein the packed column contains a matrix for causing physical perturbation of **monocytes** contained in the blood; and (c) incubating the blood after the blood has passed through the packed column for a sufficient time to allow differentiation of the **monocytes** to a dendritic cell phenotype.

12. The method of claim 11, wherein the matrix in the packed column is a plastic material.

13. The method of claim 11, wherein the matrix in the packed column is comprised of a material selected from the group consisting of sepharose, dextran, latex, cellulose acetate, acrylics, polycarbonate, polyetherimide, polysulfone, styrenes, polyurethane, polyethylene, Teflon or any combination thereof.

14. The method of claim 13, wherein the matrix is in the form of

spherical beads.

15. The method of claim 11, wherein the blood is incubated for a period of between about 1 hour and about 24 hours.

16. The method of claim 11, further comprising the steps of: (d) providing apoptotic disease effector cells; and (e) co-incubating the blood after it has passed through the packed column with the apoptotic disease effector cells.

17. The method of claim 16 wherein the disease effector cells are a CD4+ CTCL cells.

18. A method for producing functional antigen presenting dendritic cells comprising the steps of: (a) obtaining an extracorporeal quantity of a subject's blood; (b) incubating the blood with magnetic beads labeled with a molecule which attracts and binds to disease effector cells in the subject's blood; (c) loading the magnetic beads in a packed magnetic filtration column; (d) placing the packed column in a magnetic field; (e) washing the beads in the magnetic filtration column with a buffer; and (f) eluting the magnetic bead and disease effector cells from the column; (g) rendering the eluted disease effector cells apoptotic; and (h) incubating the apoptotic disease effector cells with activated **monocytes** produced using the method of claim 11.

19. The method of claim 18, wherein the disease cells are rendered apoptotic by treatment with gamma radiation, antibodies, or hot or cold shock.

20. The method of claim 18, wherein the disease effector cells are CD4+ CTCL cells and the magnetic beads are labeled with CD4ab.

21. The method of claim 18, wherein the disease effector cells are CD4+ CTCL cells and the magnetic beads are labeled with CD3ab, and the CD4+ CTCL cells are rendered apoptotic on the magnetic bead.

22. A method for producing a T-regulatory cell comprising the steps of: (a) providing a plurality of apoptotic disease effector cell-**loaded** dendritic cells; (b) providing a plurality of normal CD4+ T cells; and (c) incubating said plurality of apoptotic disease effector cell-**loaded** dendritic cells and said plurality of normal CD4+ T cells together for a period between about 1 hour to about 24 hours to allow transition of the normal CD4 T cells to a T-regulatory cell phenotype.

23. The method of claim 22, further comprising the step of administering the T-reg cells to the subject to improve the subject's immunological state.

24. The method of claim 22, wherein the said plurality of disease effector cells comprises a plurality of CD4+ CTCL cells.

L26 ANSWER 23 OF 54 USPATFULL on STN
2005:92525 Biocompatibly coated medical implants.
Rathenow, Jorg, Wiesbaden, GERMANY, FEDERAL REPUBLIC OF
Ban, Andreas, Koblenz, GERMANY, FEDERAL REPUBLIC OF
Kunstmann, Jurgen, Bad Soden, GERMANY, FEDERAL REPUBLIC OF
Mayer, Bernhard, Mainz, GERMANY, FEDERAL REPUBLIC OF
Asgari, Soheil, Munchen, GERMANY, FEDERAL REPUBLIC OF
US 2005079200 A1 20050414
APPLICATION: US 2004-938995 A1 20040910 (10)
PRIORITY: DE 2003-10322182 20030516

DE 2003-10324415 20030528
DE 2003-10333098 20030721
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A method for the production of biocompatible coatings on implantable medical devices comprising the following steps: a) at least partially coating of the medical device with a polymer film by means of a suitable coating and/or application process; b) heating of the polymer film in an atmosphere which is essentially free from oxygen to temperatures in the region of 200° C. to 2500° C., for the production of a carbon-containing layer on the medical device.

2. The method according to claim 1 wherein the implantable medical device consists of a material which is selected from carbon, carbon composite material, carbon fibre, ceramic, glass, metals, alloys, bone, stone, minerals or precursors of these or from materials which are converted under carbonisation conditions into their thermostable state.

3. The method according to claim 1 wherein the implantable medical device is selected from medical or therapeutic implants such as vascular endoprostheses, stents, coronary stents, peripheral stents, orthopaedic implants, bone or joint prostheses, artificial hearts, artificial heart valves, subcutaneous and/or intramuscular implants and such like.

4. The method according to claim 1 wherein the polymer film comprises: homopolymers or copolymers of aliphatic or aromatic polyolefins such as polyethylene, polypropylene, polybutene, polyisobutene, polypentene; polybutadiene; polyvinyls such as polyvinyl chloride or polyvinyl alcohol, poly(meth)acrylic acid, polyacrylocyano acrylate; polyacrylonitril, polyamide, polyester, polyurethane, polystyrene, polytetrafluoroethylene; polymers such as collagen, albumin, gelatine, hyaluronic acid, starch, celluloses such as methylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, carboxymethylcellulose phthalate; waxes, paraffin waxes, Fischer-Tropsch waxes; casein, dextrans, polysaccharides, fibrinogen, poly(D,L-lactides), poly(D,L-lactide coglycolides), polyglycolides, polyhydroxybutylates, polyalkyl carbonates, polyorthoesters, polyesters, polyhydroxyvaleric acid, polydioxanones, polyethylene terephthalates, polymaleate acid, polytartronic acid, polyanhydrides, polyphosphazenes, polyamino acids; polyethylene vinyl acetate, silicones; poly(ester urethanes), poly(ether urethanes), poly(ester ureas), polyethers such as polyethylene oxide, polypropylene oxide, pluronics, polytetramethylene glycol; polyvinylpyrrolidone, poly(vinyl acetate phthalate) as well as their copolymers, mixtures and combinations of these homopolymers or copolymers.

5. The method according to claim 1 wherein the polymer film comprises alkyd resin, chlorinated rubber, epoxy resin, acrylate resin, phenol resin, amine resin, melamine resin, alkyl phenol resins, epoxidised aromatic resins, oil base, nitro base, polyester, polyurethane, tar, tar-like materials, tar pitch, bitumen, starch, cellulose, waxes, shellac, organic materials of renewable raw materials or combinations thereof.

6. The method according to claim 1 wherein the polymer film is applied as a liquid polymer or polymer solution in a suitable solvent or solvent mixture, if necessary with subsequent drying, or as a polymer solid, if necessary in the form of sheeting or sprayable particles.

7. The method according to claim 6 wherein the polymer film is applied onto the device by laminating, bonding, immersing, spraying, printing,

knife application, spin coating, powder coating or flame spraying.

8. The method according to claim 1 wherein further comprising the step of depositing carbon and/or silicon by chemical or physical vapour phase deposition (CVD or PVD).

9. The method according to claim 1 wherein further comprising a sputter application of carbon and/or silicon and/or of metals.

10. The method according to claim 1 wherein the carbon-containing layer is modified by ion implantation.

11. The method according to claim 1 wherein the carbon-containing layer is post-treated with oxidising agents and/or reducing agents, preferably chemically modified by treating the coated device in oxidising acid or alkali.

12. The method according to claim 1 wherein the carbon-containing layer is purified by solvents or solvent mixtures.

13. The method according to claim 1 wherein steps a) and b) are carried out repeatedly in order to obtain a carbon-containing multi-layer coating, preferably with different porosities, by pre-structuring the polymer films or substrates or suitable oxidative treatment of individual layers.

14. The method according to claim 1 wherein several polymer film layers are applied on top of each other in step a).

15. The method according to claim 1 wherein the carbon-containing coated medical device is at least partially coated with at least one additional layer of biodegradable and/or resorbable polymers or non-biodegradable or resorbable polymers.

16. The method according to claim 15 wherein the biodegradable or resorbable polymers are selected from collagen, albumin, gelatine, hyaluronic acid, starch, celluloses such as methylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, carboxymethylcellulose phthalate; casein, dextrans, polysaccharides, fibrinogen, poly(D,L-lactides), poly(D,L-lactide coglycolides), polyglycolides, polyhydroxybutylates, polyalkyl carbonates, polyorthoesters, polyesters, polyhydroxyvaleric acid, polydioxanones, polyethylene terephthalates, polymaleate acid, polytartronic acid, polyanhydrides, polyphosphazenes, polyamino acids and their copolymers.

17. The method according to claim 1 wherein the carbon-containing coating on the device is **loaded** with at least one active principle, microorganisms or living cells.

18. The method according to claim 17 wherein the at least one active principle is applied and/or immobilised in pores on or in the coating by adsorption, absorption, physisorption, chemisorption, covalent bonding or non-covalent bonding, electrostatic fixing or occlusion.

19. The method according to claim 17 wherein the at least one active principle is immobilised essentially permanently on or in the coating.

20. The method according to claim 19 wherein the active principle comprises inorganic substances e.g. hydroxyl apatite (HAP), fluoroapatite, tricalcium phosphate (TCP), zinc; and/or organic substances such as peptides, proteins, carbohydrates such as monosaccharides, oligosaccharides and polysaccharides, lipids,

phospholipids, steroids, lipoproteins, glycoproteins, glycolipids, proteoglycanes, DNA, RNA, signal peptides or antibodies and/or antibody fragments, bioresorbable polymers, e.g. polylactonic acid, chitosan as well as pharmacologically active substances or mixtures of substances, combinations of these and such like.

21. The method according to claim 17 wherein the at least one active principle contained in or on the coating is releasable from the coating in a controlled manner.

22. The method according to claim 21 wherein the active principle releasable in a controlled manner comprises inorganic substances, e.g. hydroxyl apatite (HAP), fluoroapatite, tricalcium phosphate (TCP), zinc; and/or organic substances such as peptides, proteins, carbohydrates such as monosaccharides, oligosaccharides and polysaccharides, lipids, phospholipids, steroids, lipoproteins, glycoproteins, glycolipids, proteoglycanes, DNA, RNA, signal peptides or antibodies and/or antibody fragments, bioresorbable polymers, e.g. polylactonic acid, chitosan and pharmacologically active substances or mixtures of substances.

23. The method according claim 20 or 21 wherein the pharmacologically active substances are selected from heparin, synthetic heparin analogues (e.g. fondaparinux), hirudin, antithrombin III, drotrecogin alpha; fibrinolytics such as alteplase, plasmin, lysokinase, factor XIIa, prourokinase, urokinase, anistreplase, streptokinase; thrombocyte aggregation inhibitors such as acetyl salicylic acid, ticlopidines, clopidogrel, abciximab, dextrans; corticosteroids such as alclometasones, amcinonides, augmented betamethasones, beclomethasones, betamethasones, budesonides, cortisones, clobetasol, clocortolones, disunites, desoximetasones, dexamethasones, flucinolones, fluocinonides, flurandrenolides, flunisolides, fluticasones, halcinonides, halobetasol, hydrocortisones, methylprednisolones, mometasones, prednicarbates, prednisones, prednisolones, triamcinolones; so-called non-steroidal anti-inflammatory drugs such as diclofenac, diflunisal, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamates, mefenamic acid, meloxicam, nabumetones, naproxen, oxaprozin, piroxicam, salsalates, sulindac, tolmetin, celecoxib, rofecoxib; cytostatics such as alkaloids and podophyllum toxins such as vinblastin, vincristin; alkylants such as nitrosoureas, nitrogen lost analogues; cytotoxic antibiotics such as daunorubicin, doxorubicin and other anthracyclines and related substances, bleomycin, mitomycin; antimetabolites such as folic acid analogues, purine analogues or purimidine analogues; paclitaxel, docetaxel, sirolimus; platinum compounds such as carboplatinum, cisplatinum or oxaliplatinum; amsacrin, irinotecan, imatinib, topotecan, interferon-alpha 2a, interferon-alpha 2b, hydroxycarbamide, miltefosin, pentostatin, porfimer, aldesleukin, bexarotene, tretinoin; antiandrogens, and antiestrogens; antiarrythmics, in particular antiarrhythmics of class I such as antiarrhythmics of the quinidine type, e.g. quinidine, dysopyramide, ajmaline, prajmalium bitartrate, detajmium bitartrate; antiarrhythmics of the lidocain type, e.g. lidocain, mexiletin, phenyloin, tocainid; antiarrhythmics of class I C, e.g. propafenone, flecainide (acetate); antiarrhythmics of class II, betareceptor blockers such as metoprolol, esmolol, propranolol, metoprolol, atenolol, oxprenolol; antiarrhythmics of class III such as amiodaron, sotalol; antiarrhythmics of class IV such as diltiazem, verapamil, gallopamil; other antiarrhythmics such as adenosine, orciprenaline, ipratropium bromide; agents for stimulating angiogenesis in the myocardium such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), non-viral DNA, viral DNA, endothelial growth factors: FGF-1, FGF-2, VEGF, TGF; antibodies, monoclonal antibodies, anticalins; stem cells, endothelial progenitor cells (EPC); digitalis glycosides

such as acetyl digoxin/methyldigoxin, digitoxin, digoxin; heart glycosides such as ouabain, proscillaridin; antihypertonics such as centrally effective antiadrenergic substances, e.g. methyldopa, imidazoline receptor agonists; calcium channel blockers of the dihydropyridine type such as nifedipine, nitrendipine; ACE inhibitors: quinaprilate, cilazapril, moexipril, trandolapril, spirapril, imidapril, trandolapril; angiotensin-II-antagonists: candesartancilexetil, valsartan, telmisartan, olmesartan medoxomil, eprosartan; peripherally effective alpha-receptor blockers such as prazosin, urapidil, doxazosin, bunazosin, terazosin, indoramin; vasodilators such as dihydralazine, diisopropyl amine dichloroacetate, minoxidil, nitroprusside-sodium; other antihypertonics such as indapamide, codergocrin mesilate, dihydroergotoxin methane sulphonate, cicletanin, bosentan, fludrocortisone; phosphodiesterase inhibitors such as milrinone, enoximone and antihypotonics such as in particular adrenergics and dopaminergic substances such as dobutamine, epinephrine, etilefrine, norfenefrine, norepinephrine, oxilofrine, dopamine, midodrine, pholedrine, amezinium methyl; and partial adrenoceptor agonists such as dihydroergotamine; fibronectin, polylysines, ethylene vinyl acetates, inflammatory cytokines such as: TGFβ, PDGF, VEGF, bFGF, TNFα, NGF, GM-CSF, IGF-a, IL-1, IL-8, IL-6, growth hormones; as well as adhesive substances such as cyanoacrylates, beryllium, silica; and growth factors such as erythropoietin, hormones such as corticotropins, gonadotropins, somatropin, thyrotrophin, desmopressin, terlipressin, oxytocin, cetrorelix, corticorelin, leuprorelin, triptorelin, gonadorelin, ganirelix, buserelin, nafarelin, goserelin, as well as regulatory peptides such as somatostatin, octreotide; bone and cartilage stimulating peptides, bone morphogenetic proteins (BMPs), in particular recombinant BMPs such as e.g. recombinant human BMP-2 (rhBMP-2)), bisphosphonates (e.g. risedronates, pamidronates, ibandronates, zoledronic acid, clodronic acid, etidronic acid, alendronic acid, tiludronic acid), fluorides such as disodium fluorophosphate, sodium fluoride; calcitonin, dihydrotachystyrene; growth factors and cytokines such as epidermal growth factors (EGF), Platelet derived growth factor (PDGF), Fibroblast Growth Factors (FGFs), Transforming Growth Factors-b TGFs-b), Transforming Growth Factor-a (TGF-a), Ervthropoietin (Epo), Insulin-Like Growth Factor-I (IGF-I), Insulin-Like Growth Factor-II (IGF-II), Interleukin-1 (IL-1), Interleukin-2 (IL-2), Interleukin-6 (IL-6), Interleukin-8 (IL-8), Tumour Necrosis Factor-a (TNF-a), Tumour Necrosis Factor-b (TNF-b), Interferon-g (INF-g), Colony Stimulating Factors (CSFs); **monocyte** chemotactic protein, fibroblast stimulating factor 1, histamine, fibrin or fibrinogen, endothelin-1, angiotensin II, collagens, bromocriptin, methylsergide, methotrexate, carbontetrachloride, thioacetamide and ethanol; also silver (ions), titanium dioxide, antibiotics and antiinfectives such as in particular β-lactam antibiotics, e.g. β-lactamase-sensitive penicillins such as benzyl penicillins (penicillin G), phenoxymethylpenicillin (penicillin V); β-lactamase-resistant penicillins such as aminopenicillins such as amoxicillin, ampicillin, bacampicillin; acylaminopenicillins such as meziocillin, piperacillin; carboxypenicillins, cephalosporins such as cefazolin, cefuroxim, cefoxitin, cefotiam, cefaclor, cefadroxil, cefalexin, loracarbef, cefixim, cefuroximaxetil, ceftibutene, cefpodoximproxetil, cefpodoximproxetil; aztreonam, ertapenem, meropenem; β-lactamase inhibitors such as sulbactam, sultamicillintosilates; tetracyclines such as doxycycline, minocycline, tetracycline, chlorotetracycline, oxytetracycline; aminoglycosides such as gentamicin, neomycin, streptomycin, tobramycin, amikacin, netilmicin, paromomycin, framycetin, spectinomycin; makrolide antibiotics such as azithromycin, clarithromycin, erythromycin, roxithromycin, spiramycin, josamycin; lincosamides such as clindamycin, lincomycin, gyrase inhibitors such as fluoroquinolones such as ciprofloxacin, ofloxacin, moxifloxacin,

norfloxacin, gatifloxacin, enoxacin, fleroxacin, levofloxacin; quinolones such as pipemidic acid; sulphonamides, trimethoprim, sulphadiazin, sulphalene; glycopeptide antibiotics such as vancomycin, teicoplanin; polypeptide antibiotics such as polymyxins such as colistin, polymyxin-B nitroimidazol derivatives such as metronidazol, tinidazol; aminoquinolones such as chloroquin, mefloquin, hydroxychloroquin; biguanides such as proguanil; quinine alkaloids and diaminopyrimidines such as pyrimethamine; amphenicols such as chloramphenicol; rifabutin, dapsone, fusidinic acid, fosfomycin, nifuratel, telithromycin, fusafungin, fosfomycin, pentamidindiisethionate, rifampicin, taurolidine, atovaquone, linezolid; virostatics such as aciclovir, ganciclovir, famciclovir, foscarnet, inosine(dimepranol-4-acetamidobenzoate), valganciclovir, valaciclovir, cidofovir, brivudin; antiretroviral active principles (nucleoside analogous reverse transcriptase inhibitors and derivatives) such as lamivudin, zalcitabin, didanosine, zidovudin, tenofovir, stavudin, abacavir; non-nucleoside analogous reverse transcriptase inhibitors such as amprenavir, indinavir, saquinavir, lopinavir, ritonavir, nelfinavir; amantadine, ribavirin, zanamivir, oseltamivir and lamivudine, as well as any desired combination and mixtures thereof.

24. The method according to claim 20 or 21, characterised in that, the pharmacologically active substances are incorporated into microcapsules, liposomes, nanocapsules, nanoparticles, micelles, synthetic phospholipids, gas dispersions, emulsions, micro-emulsions, or nanospheres which are reversibly adsorbed and/or absorbed in the pores or on the surface of the carbon-containing layer for later release in the body.

25. The method according to claim 1 wherein the implantable medical device consists of a stent consisting of a material selected from the group of stainless steel, platinum-containing radiopaque steel alloys, cobalt alloys, titanium alloys, high-melting alloys based on niobium, tantalum, tungsten and molybdenum, noble metal alloys, nitinol alloys as well as magnesium alloys and mixtures of the above-mentioned substances.

26. A biocompatibly coated implantable medical device comprising a carbon-containing surface coating, produced according to the method of claim 1.

27. The device according to claim 26, wherein the device further comprises metals such as stainless steel, titanium, tantalum, platinum, nitinol or nickel-titanium alloy; carbon fibres, full carbon material, carbon composite, ceramic, glass or glass fibres.

28. The device according to claim 26, wherein the device further comprises several carbon-containing layers, preferably with different porosities.

29. The device according to claim 26, wherein the device further comprises a coating of biodegradable and/or resorbably polymers such as collagen, albumin, gelatine, hyaluronic acid, starch, celluloses such as methylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, carboxymethylcellulose phthalate; waxes, casein, dextrans, polysaccharides, fibrinogen, poly(D,L-lactides), poly(D,L-lactide coglycolides), poly(glycolides), poly(hydroxybutylates), poly(alkyl carbonates), poly(orthoesters), polyesters, poly(hydroxyvaleric acid), polydioxanones, poly(ethylene terephthalates), poly(maleate acid), poly(tartronic acid), polyanhydrides, polyphosphazenes, poly(amino acids) and their copolymers.

30. The device according to claim 26, wherein the device further

comprises a coating of non-biodegradable and/or resorbably polymers such as poly(ethylene vinyl acetate), silicones, acrylic polymers such as polyacrylic acid, polymethylacrylic acid, polyacrylocyanoacrylate; polyethylenes, polypropylenes, polyamides, polyurethanes, poly(ester urethanes), poly(ether urethane), poly(ester ureas), polyethers, poly(ethylene oxide), poly(propylene oxide), pluronics, poly(tetramethylene glycol); vinyl polymers such as polyvinylpyrrolidones, poly(vinyl alcohols)or poly(vinyl acetate phthalate) as well as their copolymers.

31. The device according to claim 26, wherein the device further comprises anionic or cationic or amphoteric coatings such as alginate, carrageenan, carboxymethylcellulose; chitosan, poly-L-lysines; and/or phosphoryl choline.

32. The device according to claim 26 wherein the carbon-containing surface coating is porous, preferably macroporous, with pore diameters in the region of 0.1 to 1000 µm, and particularly preferably nanoporous.

33. The device according to claim 26 wherein the carbon-containing surface coating is non-porous and/or essentially contains closed pores.

34. The device according to claim 26, wherein the device further comprises one or several active principles comprising inorganic substances e.g. hydroxyl apatite (HAP), fluoroapatite, tricalcium phosphate (TCP), zinc; and/or organic substances such as peptides, proteins, carbohydrates such as monosaccharides, oligosaccharides and polysaccharides, lipids, phospholipids, steroids, lipoproteins, glycoproteins, glycolipids, proteoglycanes, DNA, RNA, signal peptides or antibodies and/or antibody fragments, bioresorbable polymers, e.g. polylactonic acid, chitosan as well as pharmacologically active substances or mixtures of substances, combinations of these and such like.

35. The device according to claim 34, wherein the device further comprises a coating influencing the release of the active principles, selected from pH-sensitive and/or temperature-sensitive polymers and/or biologically active barriers such as enzymes.

36. A coated stent comprising the device of claim 26.

37. The coated stent according to claim 36, wherein the stent comprises stainless steel, preferably Fe-18Cr-14Ni-2.5Mo ("316LVM" ASTM F138), Fe-21Cr-10Ni-3.5Mn-2.5Mo (ASTM F 1586), Fe-22Cr-13Ni-5Mn (ASTM F 1314), Fe-23Mn-21Cr-1Mo-1N (nickel-free stainless steel); from cobalt alloys, preferably Co-20Cr-5W-10Ni ("L605" ASTM F90), Co-20Cr-35Ni-10Mo ("MP35N" ASTM F 562), Co-20Cr-16Ni-16Fe-7Mo ("Phynox" ASTM F 1058); from titanium alloys are CP titanium (ASTM F 67, grade 1), Ti-6Al-4V (alpha/beta ASTM F 136), Ti-6Al-7Nb (alpha/beta ASTM F1295), Ti-15Mo (beta grade ASTM F2066); from noble metal alloys, in particular iridium-containing alloys such as Pt-10Ir; nitinol alloys such as martensitic, superelastic and cold worked nitinols as well as magnesium alloys such as Mg-3Al-1Z; as well as at least one carbon-containing surface layer.

38. A coated heart valve comprising the device of claim 26.

39. The device according to claim 26 wherein the device is an orthopaedic bone prosthesis or joint prosthesis, a bone substitute or a vertebra substitute in the breast or lumbar region of the spine.

40. The device according to claim 26 wherein the device is a

subcutaneous and/or intramuscular implant for the controlled release of active principle.

L26 ANSWER 24 OF 54 USPATFULL on STN
2005:56091 Method for delivering drugs to the brain.
Rabinow, Barrett, Skokie, IL, UNITED STATES
Kipp, James E., Wauconda, IL, UNITED STATES
Gendelman, Howard, Omaha, NE, UNITED STATES
US 2005048002 A1 20050303
APPLICATION: US 2004-868680 A1 20040615 (10)
PRIORITY: US 2003-482096P 20030624 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A method for delivering a pharmaceutical composition to a brain of a mammalian subject, the method comprising the steps of: (i) providing a dispersion of the pharmaceutical composition as particles having an average particle size of from about 150 nm to about 100 microns; and (ii) administering the dispersion to the mammalian subject for delivery to the brain of a portion of the pharmaceutical composition by cells capable of reaching the brain.

2. The method of claim 1, wherein the step of administering comprises the step of administering the dispersion to a central nervous system of the mammalian subject.

3. The method of claim 1, wherein the step of administering comprises the step of administering the dispersion intrathecally, intracerebrally, epidurally or combinations thereof.

4. The method of claim 1, wherein the step of administering comprises the step of administering the dispersion to a vascular system of the mammalian subject.

5. The method of claim 4, wherein the step of administering to the vascular system comprises the step of intravenous or intra-arterial administration.

6. The method of claim 1, wherein the cells are capable of **phagocytosis**.

7. The method of claim 1, wherein the cells are selected from the group consisting of **macrophages**, **monocytes**, granulocytes, neutrophils, basophils, eosinophils and combinations thereof.

8. The method of claim 1, wherein the step of administering the dispersion comprises the step of intracellular uptake, adsorption on a surface of the cells or combinations thereof, of the pharmaceutical composition as particles by the cells.

9. The method of claim 1, wherein the step of administering the dispersion comprises the step of contacting the cells with the dispersion of the pharmaceutical composition as particles.

10. The method of claim 9, wherein the step of contacting the cells comprises the step of isolating the cells.

11. The method of claim 10, wherein the step of isolating the cells is performed by a cell separator.

12. The method of claim 1, wherein a portion of the particles do not dissolve prior to delivery to the brain.

13. The method of claim 1, wherein the dispersion has a concentration of particles above a saturation solubility of the particles.

14. The method of claim 1, wherein the pharmaceutical composition is poorly water soluble.

15. The method of claim 1, wherein the pharmaceutical composition is a therapeutic agent or a diagnostic agent.

16. The method of claim 1, wherein the pharmaceutical composition further comprises a surfactant.

17. The method of claim 16, wherein the surfactant is selected from the group consisting of anionic surfactants, cationic surfactants, zwitterionic surfactants, nonionic surfactants, surface active biological modifiers, and combinations thereof.

18. The method of claim 17, wherein the anionic surfactant is selected from the group consisting of: alkyl sulfonates, alkyl phosphates, alkyl phosphonates, potassium laurate, triethanolamine stearate, sodium lauryl sulfate, sodium dodecylsulfate, alkyl polyoxyethylene sulfates, sodium alginate, dioctyl sodium sulfosuccinate, sodium carboxymethylcellulose, bile acids and their salts, cholic acid, deoxycholic acid, glycocholic acid, taurocholic acid glycodeoxycholic acid and combinations thereof.

19. The method of claim 17, wherein the cationic surfactant is selected from the group consisting of: quaternary ammonium compounds, benzalkonium chloride, cetyltrimethylammonium bromide, lauryldimethylbenzylammonium chloride, acyl carnitine hydrochlorides, dimethyldioctadecylammomium bromide (DDAB), dioleyoltrimethylammonium propane (DOTAP), dimyristoyltrimethylammonium propane (DMTAP), dimethylaminoethanecarbamoyl cholesterol (DC-Chol), 1,2-dialkylglycero-3-alkylphosphocholine, alkyl pyridinium halides, n-octylamine, oleylamine and combinations thereof.

20. The method of claim 17, wherein the nonionic surfactant is selected from the group consisting of: glycerol esters, polyoxyethylene fatty alcohol ethers, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene fatty acid esters, sorbitan esters, glycerol monostearate, polyethylene glycols, polypropylene glycols, cetyl alcohol, cetostearyl alcohol, stearyl alcohol, aryl alkyl polyether alcohols, polyoxyethylene-polyoxypropylene copolymers, poloxamines, methylcellulose, hydroxymethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, noncrystalline cellulose, polysaccharides, starch, starch derivatives, hydroxyethylstarch, polyvinyl alcohol polyvinylpyrrolidone and combinations thereof.

21. The method of claim 17, wherein the surface active biological modifiers are selected from the group consisting of: albumin, casein, hirudin, other proteins or combinations thereof.

22. The method of claim 17, wherein the surface active biological modifiers are polysaccharides.

23. The method of claim 22, wherein the polysaccharide is selected from the group consisting of starch, heparin, chitosan and combinations thereof.

24. The method of claim 17, wherein the surfactant comprises a phospholipid.

25. The method of claim 24, wherein the phospholipid is selected from natural phospholipids, synthetic phospholipids and combinations thereof.

26. The method of claim 25, wherein the phospholipid is selected from the group consisting of: phosphatidylcholine, phosphatidylethanolamine, diacyl-glycero-phosphoethanolamine, dimyristoyl-glycero-phosphoethanolamine (DMPE), dipalmitoyl-glycero-phosphoethanolamine (DPPE), distearoyl-glycero-phosphoethanolamine (DSPE), dioleolyl-glycero-phosphoethanolamine (DOPE), phosphatidylserine, phosphatidylinositol, phosphatidylglycerol, phosphatidic acid, lysophospholipids, polyethylene glycol-phospholipid conjugates, egg phospholipid, soybean phospholipid and combinations thereof.

27. The method of claim 24, wherein the phospholipid further comprises a fimctional group to covalently link to a ligand.

28. The method of claim 27, wherein the ligand is selected from the group consisting of proteins, peptides, carbohydrates, glycoproteins, antibodies, pharmaceutically active agents and combinations thereof.

29. The method of claim 27, wherein the phospholipid comprises a pegylated phospholipid.

30. The method of claim 17, wherein the surface modifier comprises a bile acid or a salt thereof.

31. The method of claim 30, wherein the surface modifier is selected from cholic acid, deoxycholic acid, glycocholic acid, glycodeoxycholic acid, taurocholic acid, salts of these acids and combinations thereof.

32. The method of claim 1, wherein the particles in the dispersion are amorphous, semicrystalline, crystalline, or a combination thereof as determined by either differential scanning calorimetry or X-ray diffraction.

33. The method of claim 1, wherein the pharmaceutical composition is water soluble.

34. The method of claim 15, wherein the therapeutic agent is selected from the group consisting of: analgesics, anesthetics, analeptics, adrenergic agents, adrenergic blocking agents, adrenolytics, adrenocorticoids, adrenomimetics, anticholinergic agents, anticholinesterases, anticonvulsants, alkylating agents, alkaloids, allosteric inhibitors, anabolic steroids, anorexiants, antacids, antidiarrheals, antidotes, antifolics, antipyretics, antirheumatic agents, psychotherapeutic agents, neural blocking agents, anti-inflammatory agents, antihelmintics, antibiotics, anticoagulants, antidepressants, antiepileptics, antifingals, antihistamines, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, antiprotozoal agents, antiviral agents, anxiolytic sedatives, beta-adrenoceptor blocking agents, contrast media, corticosteroids, cough suppressants, diagnostic agents, diagnostic imaging agents, dopaminergics, hemostatics, hematological agents, hypnotics, immuriological agents, muscarinics, parasympathomimetics, prostaglandins, radio-pharmaceuticals, sedatives, stimulants, sympathomimetics, vitamins, xanthines, growth factors, hormones, antiprion agents and combinations thereof.

35. The method of claim 34, wherein the antineoplastic agent is selected from the group consisting of: paclitaxel and its derivative compounds, alkaloids, antimetabolites, enzyme inhibitors, alkylating agents, antibiotics and combinations thereof.

36. The method of claim 15, wherein the therapeutic agent is selected from the group consisting of carbamazepine, prednisolone and nabumetone.

37. The method of claim 15, wherein the therapeutic agent is a protease inhibitor.

38. The method of claim 37, wherein the protease inhibitor is selected from the group consisting of: indinavir, ritonavir, saquinavir, nelfinavir and combinations thereof.

39. The method of claim 15, wherein the therapeutic agent is a nucleoside reverse transcriptase inhibitor.

40. The method of claim 39, wherein the nucleoside reverse transcriptase inhibitor is selected from the group consisting of: zidovudine, didanosine, stavudine, zalcitabine, lamivudine and combinations thereof.

41. The method of claim 15, wherein the therapeutic agent is a non-nucleoside reverse transcriptase inhibitor.

42. The method of claim 41, wherein the non-nucleoside reverse transcriptase inhibitor is selected from the group consisting of efavirenz, nevirapine, delaviradine and combinations thereof.

43. The method of claim 15, wherein the therapeutic agent is used to treat central nervous system disorders.

44. The method of claim 43, wherein the central nervous system disorder is selected from the group consisting of Parkinson's disease, Alzheimer's disease, epilepsy, multiple sclerosis, amylotrophic lateral sclerosis, cerebral infarction, cerebral hemorrhage, cancer, viral infection, fungal infection, bacterial infection, and spongiform encephalopathy.

45. The method of claim 43, wherein the central nervous system disorder is HIV infection.

46. The method of claim 15, wherein the therapeutic agent is a biologic.

47. The method of claim 46, wherein the biologic is selected from the group consisting of proteins, polypeptides, carbohydrates, polynucleotides, nucleic acids and combinations thereof.

48. The method of claim 47, wherein the protein is an antibody selected from the group consisting of polyclonal antibodies, monoclonal antibodies and combinations thereof.

49. The method of claim 1, wherein the dispersion of the pharmaceutical composition is sterilized prior to administering.

50. A composition for delivery to a brain of a mammalian subject comprising a dispersion of a pharmaceutical composition provided as particles having an average particle size of from about 150 nm to about 100 microns and adapted for administering to the mammalian subject for delivery to the brain of an effective amount of the pharmaceutical composition by cells capable of reaching the brain.

51. The composition of claim 50, wherein the cells are capable of **phagocytosis**.

52. The composition of claim 50, wherein the cells are selected from the

group consisting of **macrophages**, **monocytes**, granulocytes, neutrophils, basophils, esonophils and combinations thereof.

53. The composition of claim 50, wherein the pharmaceutical composition is taken up intracellularly as particles, adsorbed as particles or combinations thereof, by the cells.

54. The composition of claim 50, wherein the pharmaceutical composition is contacted with the cells as particles.

55. The composition of claim 50, wherein the pharmaceutical composition is contacted with isolated cells.

56. The composition of claim 55, wherein the pharmaceutical composition is contacted with cells isolated by a cell separator.

57. The composition of claim 50, wherein a portion of the particles do not dissolve prior to delivery to the brain.

58. The composition of claim 50, wherein the dispersion has a concentration of particles above a saturation solubility of the particles.

59. The composition of claim 50, wherein the pharmaceutical composition is poorly water soluble.

60. The composition of claim 50, wherein the pharmaceutical composition is a therapeutic agent or a diagnostic agent.

61. The composition of claim 50, wherein the pharmaceutical composition further comprises a surfactant.

62. The composition of claim 61, wherein the surfactant is selected from the group consisting of anionic surfactants, cationic surfactants, zwitterionic surfactants, nonionic surfactants, surface active biological modifiers and combinations thereof.

63. The composition of claim 62, wherein the anionic surfactant is selected from the group consisting of: alkyl sulfonates, alkyl phosphates, alkyl phosphonates, potassium laurate, triethanolamine stearate, sodium lauryl sulfate, sodium dodecylsulfate, alkyl polyoxyethylene sulfates, sodium alginate, dioctyl sodium sulfosuccinate, sodium carboxymethylcellulose, bile acids and their salts, cholic acid, deoxycholic acid, glycocholic acid, taurocholic acid, glycodeoxycholic acid and combinations thereof.

64. The composition of claim 62, wherein the cationic surfactant is selected from the group consisting of: quaternary ammonium compounds, benzalkonium chloride, cetyltrimethylammonium bromide, lauryldimethylbenzylammonium chloride, acyl carnitine hydrochlorides, dimethyldioctadecylammomium bromide (DDAB), dioleyoltrimethylammonium propane (DOTAP), dimyristoyltrimethylammonium propane (DMTAP), dimethylaminoethanecarbamoyl cholesterol (DC-Chol), 1,2-dialkylglycero-3-alkylphosphocholine, alkyl pyridinium halides, n-octylamine, oleylamine and combinations thereof.

65. The composition of claim 62, wherein the nonionic surfactant is selected from the group consisting of: glyceryl esters, polyoxyethylene fatty alcohol ethers, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene fatty acid esters, sorbitan esters, glycerol monostearate, polyethylene glycols, polypropylene glycols, cetyl alcohol, cetostearyl alcohol, stearyl alcohol, aryl alkyl polyether

alcohols, polyoxyethylene-polyoxypropylene copolymers, poloxamines, methylcellulose, hydroxymethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, noncrystalline cellulose, polysaccharides, starch, starch derivatives, hydroxyethylstarch, polyvinyl alcohol, polyvinylpyrrolidone and combinations thereof.

66. The pharmaceutical composition of claim 62, wherein the surface active biological modifiers are selected from the group consisting of: albumin, casein, hirudin, other proteins and combinations thereof.

67. The pharmaceutical composition of claim 62, wherein the surface active biological modifiers are polysaccharides.

68. The pharmaceutical composition of claim 67, wherein the polysaccharide is selected from the group consisting of starch, heparin, chitosan and combinations thereof.

69. The composition of claim 62, wherein the surfacant comprises a phospholipid.

70. The composition of claim 69, wherein the phospholipid is selected from natural phospholipids, synthetic phospholipids and combinations thereof.

71. The composition of claim 69, wherein the phospholipid is selected from the group consisting of: phosphatidylcholine, phosphatidylethanolamine, diacyl-glycero-phosphoethanolamine, dimyristoyl-glycero-phosphoethanolamine (DMPE), dipalmitoyl-glycero-phosphoethanolamine (DPPE), distearoyl-glycero-phosphoethanolamine (DSPE), dioleolyl-glycero-phosphoethanolamine (DOPE), phosphatidylserine, phosphatidylinositol, phosphatidylglycerol, phosphatidic acid, lysophospholipids, polyethylene glycol-phospholipid conjugates,egg phospholipid, soybean phospholipid and combinations thereof.

72. The composition of claim 69, wherein the phospholipid further comprises a finctional group to covalently link to a ligand.

73. The composition of claim 72, wherein the ligand is selected from the group consisting of proteins, peptides, carbohydrates, glycoproteins, antibodies, pharmaceutically active agents and combinations thereof.

74. The composition of claim 72, wherein the phospholipid is a pegylated phospholipid.

75. The pharmaceutical composition of claim 62, wherein the surface modifier comprises a bile acid or a salt thereof.

76. The pharmaceutical composition of claim 73, wherein the surface modifier is selected from cholic acid, deoxycholic acid, glycocholic acid, glycodeoxycholic acid, taurocholic acid,salts of these acids and combinations thereof.

77. The pharmaceutical composition of claim 50, wherein the particles in the dispersion are amorphous, semicrystalline, crystalline, or a combination thereof as determined by differential scanning calorimetry or X-ray diffraction.

78. The pharmaceutical composition of claim 50, wherein the pharmaceutical composition is water soluble.

79. The pharmaceutical composition of claim 60, wherein the therapeutic

agent is selected from the group consisting of: analgesics, anesthetics, analeptics, adrenergic agents, adrenergic blocking agents, adrenolytics, adrenocorticoids, adrenomimetics, anticholinergic agents, anticholinesterases, anticonvulsants, alkylating agents, alkaloids, allosteric inhibitors, anabolic steroids, anorexiants, antacids, antidiarrheals, antidotes, antifolics, antipyretics, antirheumatic agents, psychotherapeutic agents, neural blocking agents, anti-inflammatory agents, antihelmintics, antibiotics, anticoagulants, antidepressants, antiepileptics, antifingals, antihistamines, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, antiprotozoal agents, antiviral agents, anxiolytic sedatives, beta-adrenoceptor blocking agents, contrast media, corticosteroids, cough suppressants, diagnostic agents, diagnostic imaging agents, dopaminergics, hemostatics, hematological agents, hypnotics, immuriological agents, muscarinics, parasympathomimetics, prostaglandins, radio-pharmaceuticals, sedatives, stimulants, sympathomimetics, vitamins, xanthines, growth factors, hormones, antiprion agents and combinations thereof.

80. The pharmaceutical composition of claim 79, wherein the antineoplastic agent is selected from the group consisting of: paclitaxel and its derivative compounds, alkaloids, antimetabolites, enzyme inhibitors, alkylating agents, antibiotics and combinations thereof.

81. The pharmaceutical composition of claim 60, wherein the therapeutic agent is selected from the group consisting of carbamazepine, prednisolone and nabumetone.

82. The composition of claim 60, wherein the therapeutic agent is a protease inhibitor.

83. The composition of claim 82, wherein the protease inhibitor is selected from the group consisting of: indinavir, ritonavir, saquinavir, nelfinavir and combinations thereof.

84. The composition of claim 60, wherein the therapeutic agent is a nucleoside reverse transcriptase inhibitor.

85. The composition of claim 84, wherein the nucleoside reverse transcriptase inhibitor is selected from the group consisting of: zidovudine, didanosine, stavudine, zalcitabine, lamivudine and combinations thereof.

86. The composition of claim 60, wherein the therapeutic agent is a non-nucleoside reverse transcriptase inhibitor.

87. The composition of claim 86, wherein the non-nucleoside reverse transcriptase inhibitor is selected from the group consisting of efavirenz, nevirapine, delaviradine and combinations thereof.

88. The composition of claim 60, wherein the therapeutic agent is used to treat central nervous system disorders.

89. The composition of claim 88, wherein the central nervous system disorder is selected from the group consisting of Parkinson's disease, Alzheimer's disease, epilepsy, multiple sclerosis, amyotrophic lateral sclerosis, cerebral infarction, cerebral hemorrhage, cancer, viral infection, fungal infection, bacterial infection, and spongiform encephalopathy.

90. The composition of claim 88, wherein the central nervous system

disorder is HIV infection.

91. The composition of claim 60, wherein the therapeutic agent is a biologic.

92. The composition of claim 91, wherein the biologic is selected from the group consisting of proteins, polypeptides, carbohydrates, polynucleotides, nucleic acids and combinations thereof.

93. The composition of claim 92, wherein the protein is an antibody selected from the group consisting of polyclonal antibodies, monoclonal antibodies and combinations thereof.

94. The composition of claim 50, wherein the dispersion of the pharmaceutical composition is administered intravenously, intra-arterially, intrathecally, intracerebrally, epidurally or combinations thereof.

95. The composition of claim 50, wherein the dispersion of the pharmaceutical composition is sterilized prior to administering.

96. A method for delivering a pharmaceutical composition to a brain of a mammalian subject, the method comprising the steps of: (i) isolating cells from the mammalian subject; (ii) contacting the cells with a dispersion of the pharmaceutical composition as particles having an average particle size of from about 150 nm to about 100 microns; (iii) allowing for cell uptake of a portion of the particles to form **loaded** cells; and (iv) administering to the mammalian subject the **loaded** cells to deliver a portion of the pharmaceutical composition to the brain.

97. The method of claim 96, wherein the step of administering comprises the step of administering the **loaded** cells to a central nervous system of the mammalian subject.

98. The method of claim 96, wherein the step of administering comprises the step of administering the **loaded** cells intrathecally, intracerebrally, epidurally or combinations thereof.

99. The method of claim 96, wherein the step of administering comprises the step of administering the **loaded** cells to a vascular system of the mammalian subject.

100. The method of claim 99, wherein the step of administering to the vascular system comprises the step of intravenous or intra-arterial administration, or a combination of both.

101. The method of claim 96, wherein the cells are capable of **phagocytosis**.

102. The method of claim 96, wherein the cells are selected from the group consisting of **macrophages**, **monocytes**, granulocytes, neutrophils, basophils, eosinophils and combinations thereof.

103. The method of claim 96, wherein the step of administering the dispersion comprises the step of adsorption of the pharmaceutical composition as particles on the surface of the cells.

104. The method of claim 96, wherein the step of isolating the cells is performed by a cell separator.

105. The method of claim 96, wherein a portion of the particles do not

dissolve prior to delivery to the brain.

106. The method of claim 96, wherein the dispersion has a concentration of particles above a saturation solubility of the particles.

107. The method of claim 96, wherein the pharmaceutical composition is poorly water soluble.

108. The method of claim 96, wherein the pharmaceutical composition is a therapeutic agent or a diagnostic agent.

109. The method of claim 96, wherein the pharmaceutical composition further comprises a surfactant.

110. A method of treating a patient having a central nervous system with HIV by delivering an anti-HIV composition to a brain of the patient, the method comprising the steps of: (i) providing a dispersion of the anti-HIV composition as particles having an average particle size of from about 150 nm to about 100 microns; and (ii) administering to the central nervous system of the patient the dispersion for delivery of a portion of the anti-HIV composition by **macrophages** to the brain.

111. The method of claim 110, wherein the step of administering comprises the step of administering the dispersion intravenously, intra-arterially, intrathecally, intracerebrally, epidurally or combinations thereof.

112. The method of claim 110, wherein the step of providing a dispersion comprises the step of contacting the **macrophages** to the dispersion prior to administration.

113. The method of claim 112, wherein the step of contacting the cells comprises the step of isolating the **macrophages**.

114. The method of claim 113, wherein the step of isolating comprises isolating the **macrophages** from the mammalian subject.

115. The method of claim 113, wherein the step of isolating the **macrophages** is performed by a cell separator.

116. The method of claim 110, wherein a portion of the particles do not dissolve prior to delivery to the brain.

117. The method of claim 110, wherein the dispersion has a concentration of particles above a saturation solubility of the particles.

118. The method of claim 110, wherein the step of administering comprises the step of **macrophage** uptake of the particles in the central nervous system.

119. The method of claim 110, wherein the particles further comprise a surfactant.

120. The method of claim 110, wherein the anti-HIV composition is a protease inhibitor.

121. The method of claim 120, wherein the protease inhibitor is selected from the group consisting of: indinavir, ritonavir, saquinavir, nelfinavir and combinations thereof.

122. The method of claim 110, wherein the anti-HIV composition is a nucleoside reverse transcriptase inhibitor.

123. The method of claim 122, wherein the nucleoside reverse transcriptase inhibitor is selected from the group consisting of: zidovudine, didanosine, stavudine, zalcitabine, lamivudine and combinations thereof.

124. The method of claim 110, wherein the anti-HIV composition is a non-nucleoside reverse transcriptase inhibitor.

125. The method of claim 124, wherein the non-nucleoside reverse transcriptase inhibitor is selected from the group consisting of efavirenz, nevirapine, delaviradine and combinations thereof.

L26 ANSWER 25 OF 54 USPATFULL on STN
2005:43259 Use of biologically active hiv-1 tat, fragments or derivatives thereof, to target and/or to activate antigen-presenting cells, and/or to deliver cargo molecules for preventive or therapeutic vaccination and/or to treat other diseases.
Ensoli, Barbara, Roma, ITALY
US 2005036985 A1 20050217
APPLICATION: US 2004-485180 A1 20040823 (10)
WO 2002-EP8377 20020726
PRIORITY: EP 2001-118114 20010726
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. Use of isolated native, substantially monomeric, and biologically active HIV-1 Tat, fragments or derivatives thereof, to selectively target antigen presenting cells expressing α5β1 and/or αvβ3 integrins, including dendritic cells, endothelial cells and **macrophages**, to deliver **cargo** molecules across their cellular and/or nuclear membrane and to induce their maturation and/or their antigen presenting functions.

2-55. (Canceled)

56. Method to selectively target antigen presenting cells expressing α5β1 and/or αvβ3 integrins, including dendritic cells, endothelial cells and **macrophages**, to deliver **cargo** molecules across their cellular and/or nuclear membrane and to induce their maturation and/or their antigen presenting functions said method comprising the step of putting in contact the cells with an effective amount of isolated native, substantially monomeric, and biologically active HIV-1 Tat or tat DNA, fragments and derivatives thereof.

57. Method according to claim 56 wherein isolated native, substantially monomeric, and biologically active HIV-1 Tat, fragments or derivatives thereof, will selectively target antigen presenting cells expressing α5 β1 and αvβ3 integrins, including dendritic cells, endothelial cells and **macrophages**, for the uptake of both Tat, fragments, derivatives thereof selectively bound to these cells, and **cargo** molecules bound to Tat, fragments, derivatives thereof.

58. Method according to claim 56 wherein isolated native, substantially monomeric, and biologically active HIV-1 Tat, fragments or derivatives thereof, will selectively target, bind and enter antigen presenting cells expressing the α5β1 and αvβ3 integrins, including dendritic cells, endothelial cells and **macrophages**, to induce their maturation and/or their antigen presenting functions.

59. Method according to claim 57 to selectively target antigen

presenting cells expressing α5β1 and αvβ3 integrins, or other integrins, including, but not limited to, dendritic cells, endothelial cells and **macrophages** capable of taking up Tat via the integrin-mediated pathway and/or other uptake pathways conferring a selective uptake, in order to deliver antigens and/or therapeutic compounds.

60. Method according to claim 59 wherein Tat delivers antigens in the form of peptides, proteins or DNA encoding them.

61. Method according to claim 60 wherein Tat delivers one or more antigens to induce an immune response.

62. Method according to claim 61 wherein antigens are selected among antigens from intracellular pathogens such as viruses, mycobacterium tuberculosis, candida, malaria, or from tumor cells such as those from lung, colon, breast, prostatic cancer, but specifically excluding HIV antigens Gag, Nef, Rev.

63. Method according to claim 59 wherein Tat is fused to one or more compounds selected among proteins, peptides or DNA encoding them in order to deliver such compound (s), in vitro and in vivo, intracellularly or to the cell membrane.

64. Method according to claim 63 wherein compound is one or more antigens selected among antigens from intracellular pathogens such as viruses, mycobacterium tuberculosis, candida, malaria, or from tumor cells such as those from lung, colon, breast, prostatic cancer, but specifically excluding HIV antigens Gag, Nef, Rev.

65. Method according to claim 63 wherein the compound to be fused with Tat is one or more therapeutic molecules selected among antiviral compounds, anti-inflammatory drugs, anti-angiogenic molecules, cytotoxic anti-tumor drugs, immunomodulating molecules such as chemokines or cytokines, antibodies and corresponding mixtures.

66. Method according to claim 57 wherein Tat is bound, alone or in combination with other compounds in the form of proteins, peptides or DNA encoding them, to particles such as microparticles, nanoparticles, liposomes and other particulated inert carriers and mixtures thereof.

67. Method according to claim 66 wherein compound is one or more antigens selected among antigens from intracellular pathogens such as viruses, mycobacterium tuberculosis, candida, malaria, or from tumor cells such as those from lung, colon, breast, prostatic cancer, but specifically excluding HIV antigens Gag, Nef, Rev.

68. Method according to claim 66 wherein compound is one or more therapeutic molecules selected among antiviral compounds, anti-inflammatory drugs, anti-angiogenic molecules, cytotoxic anti-tumor drugs, immunomodulating molecules such as chemokines or cytokines, antibodies and corresponding mixtures.

69. Method according to claim 66 wherein compound is one or more expression vectors.

70. Method according to claim 69 wherein the expression vector is selected among plasmid DNA, bacterial or virus vectors expressing one or more antigens.

71. Method according to claim 58 to selectively target antigen presenting cells expressing α5β1 and αvβ3

integrins or other integrins, including, but not limited to, dendritic cells, endothelial cells and **macrophages** capable of taking up Tat via the integrin-mediated pathway and/or other uptake pathways conferring a selective uptake, in order to deliver one or more antigens to enhance an immune response and to induce Th-1 type immune responses against infectious diseases and tumors.

72. Method according to claim 71 wherein Tat delivers antigens in the form of peptides, proteins or DNA encoding them.

73. Method according to claim 72 wherein Tat delivers one or more antigens to induce an immune response.

74. Method according to claim 71 wherein Tat is fused to one or more compounds selected among proteins, peptides or DNA encoding them in order to deliver such compound (s), in vitro and in vivo, intracellularly or to the cell membrane.

75. Method according to claim 74 wherein compound is one or more immunomodulating molecules, such as chemokines or cytokines, antibodies and corresponding mixtures.

76. Method according to claim 74 wherein compound is one or more antigens selected among antigens from intracellular pathogens such as viruses, mycobacterium tuberculosis, candida, malaria, or from tumor cells such as those from lung, colon, breast, prostatic cancer, but specifically excluding HIV antigens Gag, Nef, Rev.

77. Method according to claim 58 wherein Tat is bound, alone or in combination with other compounds in the form of proteins peptides or DNA encoding them, to particles such as microparticles, nanoparticles, liposomes and other particulated inert carriers and mixtures thereof.

78. Method according to claim 77 wherein compound is one or more antigens selected among antigens from intracellular pathogens such as viruses, mycobacterium tuberculosis, candida, malaria, or from tumor cells such as those from lung, colon, breast, prostatic cancer, but specifically excluding HIV antigens Gag, Nef, Rev.

79. Method according to claim 77 wherein compound is one or more immunomodulating molecules, such as chemokines or cytokines, antibodies and corresponding mixtures.

80. Method according to claim 77 wherein compound is one or more expression vectors.

81. Method according to claim 80 wherein the expression vector is selected among plasmid DNA, bacterial or virus vectors expressing one or more antigens.

82. Method for preventive and therapeutic vaccination against tumors infectious diseases said method comprising the step of administering to a subject in need an effective amount of HIV-1 Tat or tat DNA according to claim 55.

83. Method for the treatment of tumors or infectious diseases or inflammatory and angiogenic diseases said method comprising the step of administering to a subject in need an effective amount of HIV-1 Tat or tat DNA according to claim 55.

84. Method according to claim 82 wherein tat DNA is in combination with antigens selected among antigens from intracellular pathogens such as

viruses, mycobacterium tuberculosis, candida, malaria, or from tumor cells such as those from lung, colon, breast, prostatic cancer, but specifically excluding HIV antigens Gag, Nef, Rev.

85. Method according to claim 83 wherein tat DNA is in combination with antigens selected among antigens from intracellular pathogens such as viruses, mycobacterium tuberculosis, candida, malaria, or from tumor cells such as those from lung, colon, breast, prostatic cancer, but specifically excluding HIV antigens Gag, Nef, Rev.

86. Method according to claim 82 wherein tat DNA is bound, alone or in combination with other antigens DNA or therapeutic compounds to particles such as microparticles, nanoparticles, liposomes and other particulated inert carriers and mixtures thereof.

87. Method according to claim 83 wherein tat DNA is bound, alone or in combination with other antigens DNA or therapeutic compounds to particles such as microparticles, nanoparticles, liposomes and other particulated inert carriers and mixtures thereof.

88. Method according to claim 56 wherein tat DNA comprises the nucleotide sequence according to SEQ ID NO. 1, 99, or 101.

89. Method according to claim 56 wherein Tat comprises the amino acid sequence according to SEQ ID NO. 2, 100, or 102.

90. Method according to claim 56 wherein the fragments of biologically active Tat or tat DNA are selected among Tat peptides or corresponding tat DNA comprising, alone or associated, the RGD domain, the cystein-rich domain, the basic domain.

91. Method according to claim 90 wherein the fragments are combined with other HIV-1 Tat peptides or corresponding tat DNA comprising the core domain: aa 38 to 47 in the HTLV-IIIB, clone BH-10, and/or the amminoterminal region aa 1 to 20 in the HTLV-IIIB, clone BH-10.

92. Method according to claim 90 wherein the RGD domain comprises: aa 73 to 86 in the HTLV-IIIB, clone BH-10, aa 74 to 84, aa 75 to 83, aa 76 to 82, aa 77 to 81, aa 77 to 82, aa 77 to 83, aa 76 to 83; the cystein-rich domain comprises: aa 22 to 37 in the HTLV-IIIB, clone BH-10; the basic domain comprises: aa 48 to 61 in the HTLV-IIIB, clone BH-10, and all their corresponding nucleotide sequences.

93. Method according to claim 56 wherein the fragments of biologically active Tat or tat DNA are selected among any HIV variant (HIV-1, HIV-2 and other HIV types and subtypes) that contain one or more T-cell epitopes in their amino acid sequences or corresponding nucleotide sequence HTLV-IIIB, clone BH-10 or 89.6.

94. Method according to claim 56 wherein the derivatives of Tat or tat DNA comprise Tat mutants of the HTLV-IIIB, clone BH-10, variant, selected among that ones comprising the amino acid sequence or corresponding nucleotide sequences, of cys22 and/or lys41.

95. Pharmaceutical composition comprising as active principle an effective amount of biologically active HIV Tat or tat DNA, fragments or derivative thereof, combined or fused with at least one of the following: antigens, therapeutic compounds, adjuvants, support particles, for preventive and therapeutic vaccination against infectious diseases and tumors or for the treatment of a disease selected among infectious diseases, inflammatory and angiogenic diseases, tumors.

96. Pharmaceutical composition according to claim 95 wherein the antigen is selected among antigens from intracellular pathogens such as viruses, mycobacterium tuberculosis, candida, malaria, or from tumor cells such as those from lung, colon, breast, prostatic cancer, but specifically excluding HIV antigens Gag, Nef, Rev.

97. Pharmaceutical composition according to claim 95 wherein the therapeutic compound is selected among antiviral compounds, anti-inflammatory drugs, anti-angiogenic molecules, cytotoxic anti-tumor drugs, immunomodulating molecules such as chemokines or cytokines, antibodies and corresponding mixtures.

98. Pharmaceutical composition according to claim 95 wherein the support particles are selected among: microparticles, nanoparticles, liposomes and other particulated delivery systems and mixtures thereof.

99. Pharmaceutical composition according to claim 95 wherein the adjuvant is selected among Alum, RIBI, ISCOMS, CpG sequence, Lipopeptides and corresponding mixtures.

100. Pharmaceutical composition according to claim 95 wherein the infectious disease is selected among those infections caused by human or animal viruses, bacteria or other intracellular and extracellular pathogens, including sexual infectious diseases, endocarditis, urinary tract infections, osteomyelitis, cutaneous infections, or streptococcus and staphylococcus infections, pneumococcus infections, tetanus, meningococcus infections, tuberculosis, malaria, candidosis, infections by Helicobacter, salmonella, syphilis, herpetic infections, including varicella, mononucleosis and Epstein-Barr-derived infections, human herpesvirus-8 infection, cytomegalovirus, herpes labialis and genitalis, hepatitis virus infection (A, B, C, D, G), papilloma virus-derived infections, influenza, lysteria, vibrio cholerae.

101. Pharmaceutical composition according to claim 95 wherein the inflammatory disease is an allergy or inflammation associated or not with a viral, bacterial or parasitic infection, including immune-mediated cutaneous diseases, Lupus erythematous systemic, rheumatoid arthritis, systemic sclerosis, dermatomiositis, Sjogren syndrome, Goodpasture syndrome, vasculitis, sarcoidosis, osteoarthrosis, infectious arthritis, psoriasis, Chron disease, rectocolitis ulcerosus, tyroiditis, scleroderma, allergic diseases.

102. Pharmaceutical composition according to claim 95 wherein the angiogenic disease is selected among non-neoplastic angioproliferative diseases including diabetic retinopathy, retrolental fibroplasia, trachoma, vascular glaucoma, immune inflammation, non-immune inflammation, atherosclerosis, excessive wound repair, angiodermatitis, colon angiodisplasia, angioedema and angiofybromas.

103. Pharmaceutical composition according to claim 95 wherein the tumor is selected among benign and malignant tumors including tumors of soft tissues, bones, cartilages and blood, such as, but not limited to, Kaposi's sarcoma and other neoplasia of the skin, lung, breast, gut, liver, pancreas, endocrine system, uterus, ovary, sarcomas, acute and chronic leukemia, and neoplasia of lymphatic cells.

104. Pharmaceutical composition according to claim 95 further comprising adjuvants, diluents, eccipients, carriers.

105. Pharmaceutical composition according to claim 95 in the form of tablets, pills, sprays, injectable solutions, suspensions, powders, creams, ointments.

106. Pharmaceutical composition according to claim 95 administered by the parenteral: subcute, intramuscular, intradermic; or mucosal: vaginal, rectal, oral, nasal; or topic route.

L26 ANSWER 26 OF 54 USPATFULL on STN
2005:38451 Analyte measuring device.
Shults, Mark C., Madison, WI, UNITED STATES
Brauker, James H., San Diego, CA, UNITED STATES
Carr-Brendel, Victoria, Pleasanton, CA, UNITED STATES
Tapsak, Mark, Orangeville, PA, UNITED STATES
Markovic, Dubravka, San Diego, CA, UNITED STATES
Updike, Stuart J., Madison, WI, UNITED STATES
Rhodes, Rathbun K., Madison, WI, UNITED STATES
US 2005033132 A1 20050210
APPLICATION: US 2004-846150 A1 20040514 (10)
PRIORITY: US 2003-472673P 20030521 (60)
US 2004-544722P 20040212 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A device for subcutaneous monitoring of glucose levels, comprising a housing and a sensor, the sensor comprising an angiogenic layer for promoting adequate microcirculatory delivery of glucose and oxygen to the sensor, wherein the angiogenic layer further comprises a bioactive agent.

2. The device of claim 1, wherein the device is sized and configured for wholly subcutaneous implantation.

3. The device of claim 1, wherein the angiogenic layer comprises a material selected from the group consisting of hydrophilic polyvinylidene fluoride, mixed cellulose esters, polyvinyl chloride, polyvinyl alcohol, polyethylene, polytetrafluoroethylene, cellulose acetate, cellulose nitrate, polycarbonate, nylon, polyester, mixed esters of cellulose polyvinylidene difluoride, silicone, polyacrylonitrile, polypropylene, polysulfone, polymethacrylate, and mixtures thereof.

4. The device of claim 3, wherein the angiogenic layer comprises expanded polytetrafluoroethylene.

5. The device of claim 3, wherein the angiogenic layer comprises silicone.

6. The device of claim 1, wherein the bioactive agent is selected from the group consisting of anti-inflammatory agents, anti-infective agents, anesthetics, inflammatory agents, growth factors, immunosuppressive agents, antiplatelet agents, anticoagulants, ACE inhibitors, cytotoxic agents, anti-barrier cell compounds, vascularization-inducing compounds, anti-sense molecules, and mixtures thereof.

7. The device of claim 6, wherein the bioactive agent is an anti-inflammatory agent selected from the group consisting of nonsteroidal anti-inflammatory drugs (NTHEs), aspirin, celecoxib, choline magnesium trisalicylate, diclofenac potasium, diclofenac sodium, diflunisal, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, melenamic acid, nabumetone, naproxen, naproxen sodium, oxaprozin, piroxicam, rofecoxib, salsalate, sulindac, tolmetin, corticosteroids, cortisone, hydrocortisone, methylprednisolone, prednisone, prednisolone, betamethesone, beclomethasone dipropionate,

budesonide, dexamethasone sodium phosphate, flunisolide, fluticasone propionate, triamcinolone acetonide, betamethasone, fluocinolone, fluocinonide, betamethasone dipropionate, betamethasone valerate, desonide, desoximetasone, fluocinolone, triamcinolone, triamcinolone acetonide, clobetasol propionate, dexamethasone, and mixtures thereof.

8. The device of claim 6, wherein the bioactive agent is an anti-infective agent selected from the group consisting of anthelmintics, mebendazole, antibiotics, aminoclycosides, gentamicin, neomycin, tobramycin, antifungal antibiotics, amphotericin b, fluconazole, griseofulvin, itraconazole, ketoconazole, nystatin, micatin, tolnaftate, cephalosporins, cefaclor, cefazolin, cefotaxime, ceftazidime, ceftriaxone, cefuroxime, cephalexin, beta-lactam antibiotics, cefotetan, meropenem, chloramphenicol, macrolides, azithromycin, clarithromycin, erythromycin, penicillins penicillin G sodium salt, amoxicillin, ampicillin, dicloxacillin, nafcillin, piperacillin, ticarcillin, tetracyclines, doxycycline, minocycline, tetracycline, bacitracin, clindamycin, colistimethate sodium, polymyxin b sulfate, vancomycin; antivirals including acyclovir, amantadine, didanosine, efavirenz, foscarnet, ganciclovir, indinavir, lamivudine, nelfinavir, ritonavir, saquinavir, stavudine, valacyclovir, valganciclovir, zidovudine, quinolones, ciprofloxacin, levofloxacin, sulfonamides, sulfadiazine, sulfisoxazole, sulfones, dapsone, furazolidone, metronidazole, pentamidine, sulfanilamidum crystallinum, gatifloxacin, sulfamethoxazole/trimethoprim, and mixtures thereof.

9. The device of claim 6, wherein the bioactive agent is an anesthetic selected from the group consisting of ethanol, bupivacaine, chloroprocaine, levobupivacaine, lidocaine, mepivacaine, procaine, ropivacaine, tetracaine, desflurane, isoflurane, ketamine, propofol, sevoflurane, codeine, fentanyl, hydromorphone, marcaine, meperidine, methadone, morphine, oxycodone, remifentanil, sufentanil, butorphanol, nalbuphine, tramadol, benzocaine, dibucaine, ethyl chloride, xylocaine, phenazopyridine, and mixtures thereof.

10. The device of claim 1, wherein the bioactive agent is selected from the group. consisting of S1P, monobutyrin, Cyclosporin A, Anti-thrombospondin-2, Rapamycin, Dexamethasone, Super Oxide Dismutase (SOD) Mimetic Compounds, Lipopolysaccharide, angiogenic lipid product of adipocytes, Sphingosine-1-Phosphate, Thrombospondin-2 antisense, and mixtures thereof.

11. The device of claim 1, wherein the bioactive agent is incorporated within the angiogenic layer by absorption into the angiogenic layer.

12. The device of claim 1, wherein the bioactive agent is incorporated within the angiogenic layer during formation of the angiogenic layer.

13. The device of claim 1, wherein the bioactive agent is incorporated within the angiogenic layer using a microcapsule agent.

14. The device of claim 1, wherein the bioactive agent is incorporated within the angiogenic layer using a carrier agent.

15. The device of claim 1, wherein the bioactive agent is incorporated in the angiogenic layer using at least one substance selected from the group consisting of an ionic surfactant, a nonionic surfactant, a detergent, an emulsifier, a demulsifier, a stabilizer, an aqueous carrier, an oleaginous carrier, a solvent, a preservative, an antioxidant, a buffering agent, and mixtures thereof.

16. The device of claim 1, wherein the angiogenic layer comprises a

plurality of pores and wherein the bioactive agent is contained within the pores of the angiogenic layer.

17. The device of claim 1, the sensor further comprising a membrane impregnated with an oxidase.

18. The device of claim 17, wherein the oxidase impregnated membrane comprises a resistance layer, an enzyme layer, an interference layer, and an electrolyte layer.

19. The device of claim 17, wherein the oxidase impregnated membrane comprises a single homogeneous structure.

20. The device of claim 18, wherein the resistance layer restricts transport of glucose therethrough.

21. The device of claim 18, wherein the resistance layer comprises a polymer membrane with an oxygen-to-glucose permeability ratio of at least about 100:1.

22. The device of claim 18, wherein the interference layer comprises a hydrophobic membrane substantially permeable to hydrogen peroxide.

23. The device of claim 18, wherein the interference layer comprises a hydrophobic membrane substantially impermeable to at least one substance having a molecular weight substantially greater than hydrogen peroxide.

24. The device of claim 18, wherein the electrolyte layer comprises a semipermeable hydrophilic coating.

25. The device of claim 18, wherein the electrolyte layer comprises a curable copolymer of a urethane polymer and a hydrophilic film-forming polymer.

26. The device of claim 18, wherein the enzyme layer comprises glucose oxidase.

27. The device of claim 1, wherein the housing comprises an electronic circuit and at least two electrodes operatively connected to the electronic circuit, and wherein the sensor is operably connected to the electrodes of the housing.

28. The device of claim 27, wherein the housing comprises a data transmitting apparatus operatively connected to the electronic circuit for transmitting data to a location external to the device.

29. The device of claim 28, wherein the data transmitting apparatus comprises radiotelemetry.

30. The device of claim 1, wherein the sensor is located at an apex of the housing.

31. The device of claim 1, wherein the sensor comprises a dome configuration on at least a portion thereof.

32. A device for subcutaneous monitoring of a glucose level, comprising a housing and a sensor, the sensor comprising a first domain, a second domain, and a bioactive agent; wherein the first domain supports tissue ingrowth and is positioned more distal to the housing than the second domain; wherein the second domain is substantially impermeable to **macrophages** and is situated between the first domain and the housing, and wherein the bioactive agent is incorporated within at least one of

the first domain, the second domain, and the sensor.

33. The device of claim 32, wherein the device is sized and configured for wholly subcutaneous implantation.

34. The device of claim 32, wherein the first domain comprises a material selected from the group consisting of hydrophilic polyvinylidene fluoride, mixed cellulose esters, polyvinyl chloride, polyethylene, polyvinyl alcohol, polytetrafluoroethylene, expanded polytetrafluoroethylene, cellulose acetate, cellulose nitrate, polycarbonate, nylon, polyester, mixed esters of cellulose polyvinylidene difluoride, silicone, polyacrylonitrile, polypropylene, polysulfone, polymethacrylate, and mixtures thereof.

35. The device of claim 32, wherein the bioactive agent is selected from the group consisting of anti-inflammatory agents, anti-infective agents, anesthetics, inflammatory agents, growth factors, immunosuppressive agents, antiplatelet agents, anticoagulants, ACE inhibitors, cytotoxic agents, anti-barrier cell compounds, vascularization-inducing compounds, anti-sense molecules, and mixtures thereof.

36. The device of claim 35, wherein the bioactive agent is an anti-inflammatory agent selected from the group consisting of nonsteroidal anti-inflammatory drugs (NTHEs), aspirin, celecoxib, choline magnesium trisalicylate, diclofenac potasium, diclofenac sodium, diflunisal, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, melenamic acid, nabumetone, naproxen, naproxen sodium, oxaprozin, piroxicam, rofecoxib, salsalate, sulindac, tolmetin, corticosteroids, cortisone, hydrocortisone, methylprednisolone, prednisone, prednisolone, betamethesone, beclomethasone dipropionate, budesonide, dexamethasone sodium phosphate, flunisolide, fluticasone propionate, triamcinolone acetonide, betamethasone, fluocinolone, fluocinonide, betamethasone dipropionate, betamethasone valerate, desonide, desoximetasone, fluocinolone, triamcinolone, triamcinolone acetonide, clobetasol propionate, dexamethasone, and mixtures thereof.

37. The device of claim 35, wherein the bioactive agent is an anti-infective agent selected from the group consisting of anthelmintics, mebendazole, antibiotics, aminoclycosides, gentamicin, neomycin, tobramycin, antifungal antibiotics, amphotericin b, fluconazole, griseofulvin, itraconazole, ketoconazole, nystatin, micatin, tolnaftate, cephalosporins, cefaclor, cefazolin, cefotaxime, ceftazidime, ceftriaxone, cefuroxime, cephalexin, beta-lactam antibiotics, cefotetan, meropenem, chloramphenicol, macrolides, azithromycin, clarithromycin, erythromycin, penicillins penicillin G sodium salt, amoxicillin, ampicillin, dicloxacillin, nafcillin, piperacillin, ticarcillin, tetracyclines, doxycycline, minocycline, tetracycline, bacitracin, clindamycin, colistimethate sodium, polymyxin b sulfate, vancomycin; antivirals including acyclovir, amantadine, didanosine, efavirenz, foscarnet, ganciclovir, indinavir, lamivudine, nelfinavir, ritonavir, saquinavir, stavudine, valacyclovir, valganciclovir, zidovudine; quinolones, ciprofloxacin, levofloxacin, sulfonamides, sulfadiazine, sulfisoxazole, sulfones, dapsone, furazolidone, metronidazole, pentamidine, sulfanilamidum crystallinum, gatifloxacin, and sulfamethoxazole/trimethoprim.

38. The device of claim 35, wherein the bioactive agent is an anesthetic selected from the group consisting of ethanol, bupivacaine, chloroprocaine, levobupivacaine, lidocaine, mepivacaine, procaine, ropivacaine, tetracaine, desflurane, isoflurane, ketamine, propofol, sevoflurane, codeine, fentanyl, hydromorphone, marcaine, meperidine, methadone, morphine, oxycodone, remifentanil, sufentanil, butorphanol,

nalbuphine, tramadol, benzocaine, dibucaine, ethyl chloride, xylocaine, phenazopyridine, and mixtures thereof.

39. The device of claim 32, wherein the bioactive agent is selected from the group consisting of S1P, monobutyrin, Cyclosporin A, Anti-thrombospondin-2, Rapamycin, Dexamethasone, Super Oxide Dismutase (SOD) Mimetic Compounds, Lipopolysaccharide, angiogenic lipid product of adipocytes, Sphingosine-1-Phosphate, Thrombospondin-2 antisense, and mixtures thereof.

40. The device of claim 32, wherein the bioactive agent is incorporated within the first domain by absorption.

41. The device of claim 32, wherein the bioactive agent is incorporated within the second domain by absorption.

42. The device of claim 32, wherein the bioactive agent is **loaded** into at least one of the first domain, the second domain, and the sensor using a microcapsule agent.

43. The device of claim 32, wherein the bioactive agent is **loaded** is **loaded** into at least one of the first domain, the second domain, and the sensor using a carrier agent.

44. The device of claim 32, wherein the bioactive agent is incorporated into the vascular promotion layer using at least one substance selected from the group consisting of an ionic surfactant, a nonionic surfactant, a detergent, an emulsifier, a demulsifier, a stabilizer, an aqueous carrier, an oleaginous carrier, a solvent, a preservative, an antioxidant, a buffering agent, and mixtures thereof.

45. The device of claim 32, wherein the first domain comprises a plurality of pores and wherein the vascular promotion layer comprises the bioactive agent contained within the pores of the angiogenic layer.

46. The device of claim 32, the sensor further comprising a membrane impregnated with an oxidase.

47. The device of claim 46, wherein the oxidase impregnated membrane comprises a resistance layer, an enzyme layer, an interference layer, and an electrolyte layer.

48. The device of claim 46, wherein the oxidase impregnated membrane comprises a single homogeneous structure.

49. The device of claim 47, wherein the resistance layer restricts transport of glucose therethrough.

50. The device of claim 47, wherein the resistance layer comprises a polymer membrane with an oxygen-to-glucose permeability ratio of at least about 100:1.

51. The device of claim 47, wherein the interference layer comprises a hydrophobic membrane substantially permeable to hydrogen peroxide.

52. The device of claim 47, wherein the interference layer comprises a hydrophobic membrane substantially impermeable to substances having a molecular weight substantially greater than hydrogen peroxide.

53. The device of claim 47, wherein the electrolyte layer comprises a semipermeable hydrophilic coating.

54. The device of claim 47, wnerein the electrolyte layer comprises a curable copolymer of a urethane polymer and a hydrophilic film-forming polymer.

55. The device of claim 47, wherein the enzyme layer comprises glucose oxidase.

56. The device of claim 32, wherein the housing comprises an electronic circuit and at least two electrodes operatively connected to the electronic circuit, and wherein the sensor is operably connected to the electrodes of the housing.

57. The device of claim 56, wherein the housing comprises a data transmitting apparatus operatively connected to the electronic circuit for transmitting data to a location external to the device.

58. The device of claim 57, wherein the data transmitting apparatus comprises radiotelemetry.

59. The device of claim 32, wherein the sensor is located at an apex of the housing.

60. The device of claim 32, wherein the sensor comprises a dome configuration on at least a portion thereof.

61. A device for subcutaneous monitoring of glucose levels, comprising a housing, a sensor, and an an angiogenic layer for promoting adequate microcirculatory delivery of glucose and oxygen to the sensor, wherein the angiogenic layer is configured to promote vascularization in or around the angiogenic layer so as to maintain sufficient blood flow to the sensor for glucose measurement thereby.

62. The device of claim 61, wherein the device is sized and configured for wholly subcutaneous implantation.

63. The device of claim 61, wherein the angiogenic layer comprises a material selected from the group consisting of hydrophilic polyvinylidene fluoride, mixed cellulose esters, polyvinyl chloride, polyvinyl alcohol, polyethylene, polytetrafluoroethylene, cellulose acetate, cellulose nitrate, polycarbonate, nylon, polyester, mixed esters of cellulose polyvinylidene difluoride, silicone, polyacrylonitrile, polypropylene, polysulfone, polymethacrylate, and mixtures thereof.

64. The device of claim 63, wherein the angiogenic layer comprises expanded polytetrafluoroethylene.

65. The device of claim 63, wherein the angiogenic layer comprises silicone.

66. The device of claim 61, the sensor further comprising a membrane impregnated with an oxidase.

67. The device of claim 66, wherein the oxidase impregnated membrane comprises a resistance layer, an enzyme layer, an interference layer, and an electrolyte layer.

68. The device of claim 66, wherein the oxidase impregnated membrane comprises a single homogeneous structure.

69. The device of claim 67, wherein the resistance layer restricts transport of glucose therethrough.

70. The device of claim 67, wherein the resistance layer comprises a polymer membrane with an oxygen-to-glucose permeability ratio of at least about 100:1.

71. The device of claim 67, wherein the interference layer comprises a hydrophobic membrane substantially permeable to hydrogen peroxide.

72. The device of claim 67, wherein the interference layer comprises a hydrophobic membrane substantially impermeable to at least one substance having a molecular weight substantially greater than hydrogen peroxide.

73. The device of claim 67, wherein the electrolyte layer comprises a semipermeable hydrophilic coating.

74. The device of claim 67, wherein the electrolyte layer comprises a curable copolymer of a urethane polymer and a hydrophilic film-forming polymer.

75. The device of claim 67, wherein the enzyme layer comprises glucose oxidase.

76. The device of claim 61, wherein the housing comprises an electronic circuit and at least two electrodes operatively connected to the electronic circuit, and wherein the sensor is operably connected to the electrodes of the housing.

77. The device of claim 76, wherein the housing comprises a data transmitting apparatus operatively connected to the electronic circuit for transmitting data to a location external to the device.

78. The device of claim 77, wherein the data transmitting apparatus comprises radiotelemetry.

79. The device of claim 61, wherein the sensor is located at an apex of the housing.

80. The device of claim 61, wherein the sensor comprises a dome configuration on at least a portion thereof.

L26 ANSWER 27 OF 54 USPATFULL on STN
2004:326889 Cytotoxic T-cell epitopes of papillomavirus L1 protein and their use in diagnostics and therapy.
Jochmus, Ingrid, Grobenzell, GERMANY, FEDERAL REPUBLIC OF
Nieland, John, Munchen, GERMANY, FEDERAL REPUBLIC OF
US 2004258708 A1 20041223
APPLICATION: US 2004-890526 A1 20040713 (10)
PRIORITY: DE 1999-19925199 19990601
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1-27. (Cancelled)

28. A T-cell epitope having an amino acid sequence ILVPKVSGL, RLVWACVGV, HLFNRAGTV, YLRREQMFV, TLQANKSEV, ILEDWNFGL, SLWLPSEATVYL, NLASSNYFPT, TLTADVMTYI, YLPPVPVSKV, YDLQFIFQL, FYNPDTQRL, MHGDTPTLH, ETTDLYCY, QAEPDRAHYN, SMVTSDAQI, and/or a functionally active variant thereof.

29. The T-cell epitope as claimed in claim 28, wherein said variant has a sequence homology to ILVPKVSGL, RLVWACVGV, HLFNRAGTV, YLRREQMFV, TLQANKSEV, ILEDWNFGL, SLWLPSEATVYL, NLASSNYFPT, TLTADVMTYI, YLPPVPVSKV,

YDLQFIFQL, FYNPDTQRL, MHGDTPTLH, ETTDLYCY, QAEPDRAHYN or SMVTSDAQI of at least approx. 65%, preferably at least approx. 75% and in particular at least approx. 85% at the amino acid level.

30. The T-cell epitope as claimed in claim 28, wherein said variant is structurally homologous to ILVPKVSGL, RLVWACVGV, HLFNRAGTV, YLRREQMFV, TLQANKSEV, ILEDWNFGL, SLWLPSEATVYL, NLASSNYFPT, TLTADVMTYI, YLPPVPVSKV, YDLQFIFQL, FYNPDTQRL, MHGDTPTLH, ETTDLYCY, QAEPDRAHYN or SMVTSDAQI.

31. The T-cell epitope as claimed in claim 28, wherein the T-cell epitope is a cytotoxic T-cell epitope.

32. A compound comprising a T-cell epitope as claimed in claim 28, wherein the compound is not a naturally occurring L1 protein of a papillomavirus and not an exclusively N-terminal or an exclusively C-terminal deletion mutant of a naturally occurring L1 protein of a papillomavirus.

33. The compound as claimed in claim 32, wherein the compound is a polypeptide, in particular a fusion protein.

34. The compound as claimed in claim 32, wherein the compound is a polypeptide of at least 50 amino acids in length.

35. The compound as claimed in claim 32, wherein the compound is a polypeptide of at least 35 amino acids in length.

36. The compound as claimed in claim 32, wherein the compound is a polypeptide of at least approx. 20 amino acids in length.

37. The compound as claimed in claim 32, wherein the compound is a polypeptide of at least 9-13 amino acids in length.

38. The compound as claimed in claim 32, wherein the compound contains a label selected from the group consisting of a chemical, radioactive, nonradioactive isotope and fluorescent label.

39. A nucleic acid, wherein the nucleic acid codes for a T-cell epitope as claimed in claim 32.

40. A vector containing a nucleic acid as claimed in claim 39.

41. A cell containing at least one T-cell epitope as claimed in claim 32.

42. The cell as claimed in claim 41, wherein the cell is transfected, transformed, or infected with a nucleic acid as claimed in claim 39.

43. The cell as claimed in claim 41, wherein the cell was incubated with at least one compound as claimed in claim 32.

44. The cell as claimed in claim 41, wherein the cell is selected from the group consisting of a B cell, a **macrophage**, a dendritic cell, a fibroblast, in particular a JY, T2, CaSki cell and EBV-transformed cell.

45. A complex comprising a T-cell epitope as claimed in claim 28 and at least one further compound.

46. The complex as claimed in claim 45, wherein the complex contains at least one MHC class I molecule.

47. The complex as claimed in claim 46, wherein the complex contains a

human MHC class I molecule

48. The complex as claimed in claim 46, wherein the MHC class I molecule is a HLA A2.01 molecule.

49. A method for in vitro detection of the activation of T cells by at least one compound containing a T-cell epitope as claimed in claim 28, which comprises the following steps: a) stimulating cells using at least one said compound; b) adding at least one target cell presenting a T-cell epitope as claimed in claims 28 or a complex as claimed in claim 45, and c) determining T-cell activation.

50. The method as claimed in claim 49, wherein it comprises, after step a), the following additional step a'): a') coculturing of the cells for at least 1 week with a substance selected from the group consisting of: (i) at least one target cell **loaded** with a substance selected from the group consisting of a compound as claimed in claim 32, at least one complex as claimed in claim 45, at least one capsomer, at least one stable capsomer, at least one VLP, at least one CVLP, and at least one virus, (ii) at least one complex as claimed in claim 45, and (iii) at least one target cell presenting a T-cell epitope as claimed in claim 28, prior to step b).

51. A method for producing a target cell as claimed in claim 41, wherein the target cell is incubated with at least one compound as claimed in claim 32.

52. A method for producing a target cell as claimed in claim 41, wherein the target cells is transfected, transformed or infected with a nucleic acid as claimed in claim 39.

53. A method for producing a target cell as claimed in claim 51 or 52, wherein the target cell is selected from the group consisting of a B cell, a **macrophage**, a dendritic cell, a fibroblast, in particular a JY, T2, CaSki cell and EBV-transformed cell.

54. The method as claimed in claim 29, wherein instead of step a) the following step a") is carried out: a") producing and preparing samples containing T cells and subsequent culturing.

55. An assay system for in vitro detection of the activation of T cells, comprising: a) a substance selected from the group consisting of at least one T-cell epitope as claimed in claim 28, at least one compound as claimed in claim 32, at least one vector as claimed in claim 40, at least one cell as claimed in claim 41, and at least one complex as claimed in claim 45, and b) effector cells selected from the group consisting of the immune system, T cells, cytotoxic T cells and T helper cells.

56. A method of causing or detecting an immune response using a substance selected form the group consisting of at least one T-cell epitope as claimed in claim 28, at least one compound as claimed in claim 32, at least one vector as claimed in claim 40, at least one cell as claimed in claim 41, and at least one complex as claimed in claim 45.

57. A medicament or diagnostic agent, comprising a substance selected from the group consisting of at least one compound as claimed in claim 32, at least one vector as claimed in claim 40, at least one cell as claimed in claim 41, and at least one complex as claimed in claim 45.

58. The medicament or diagnostic agent as claimed in claim 57, wherein a substance selected from the group consisting of at least one compound as

claimed in claim 32, at least one vector as claimed in claim 40, at least one cell as claimed in claim 41, and at least one complex as claimed in claim 45 is present in solution, bound to a solid matrix or mixed with an adjuvant.

L26 ANSWER 28 OF 54 USPATFULL on STN
2004:320921 Method for producing ready to use, antigen loaded or unloaded, cryconserved mature dendritic cells.
Schuler, Gerold, Spardorf, GERMANY, FEDERAL REPUBLIC OF
Schuler-Thurner, Beatrice, Saprdorf, GERMANY, FEDERAL REPUBLIC OF
US 2004253574 A1 20041216
APPLICATION: US 2003-362715 A1 20030625 (10)
WO 2001-EP9790 20010824
PRIORITY: DE 2000-10041515 20000824
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A method for the preparation of ready-for-use cryoconserved mature dendritic cells, the method comprising: (a) providing immature dendritic cells (DC); (b) culturing the immature DCs in a culture medium containing a maturing cocktail comprising one or more maturing stimulants to obtain mature DCs; and (c) freezing the mature DCs in a freezing medium which does not contain any heterologous serum.

2. The method according to claim 1, wherein said immature dendritic cells (DCs) are **loaded** with an antigen or antigen-antibody complex prior to said freezing.

3. The method according to claim 1, wherein said immature dentritic cells (DCs) are prepared from CD14+ mononuclear cells (**monocytes**).

4. The method according to claim 1, wherein said maturing stimulants are selected from the group consisting of IL-1, IL-6, TNF-α, prostaglandins, IFN-α, lipopolysaccharides and other bacterial cell products, phosphorylcholine, calcium ionophores, phorbol esters, heat-shock proteins, nucleotides, lipopeptides, artificial ligands for Toll-like receptors, double-stranded RNA, immunostimulant DNA sequences, and CD40 ligand.

5. The method according to claim 4, wherein said dendritic cells (DCs) are cultured in the presence of from 0.1 to 100 ng/ml IL-1β, from 0.1 to 100 ng/ml IL-6, from 0.1 to 10 μg/ml prostaglandin E2 (PGE2), and from 0.1 to 100 ng/ml TNF-α.

6. The method according to claim 4, wherein the maturing stimulants IL-1β, IL-6, prostaglandin E2 (PGE2), and TNFα are derived from purified formulations of the individual maturing stimulants.

7. The method according to claim 1, wherein the culturing is performed for at least one hour.

8. The method according to claim 1, wherein said freezing medium contains: (i) from 5 to 25% (v/v) of one or more cryoprotectants, (ii) from 2 to 30% (w/v) of one or more polyol compounds and (iii) from 2 to 90% (w/v) of a non-heterologous serum component.

9. The method according to claim 1, wherein the cells are frozen in a concentration of from 5x106 to 100x106 cells/ml.

10. (Canceled).

11. The method according to claim 2, wherein said antigen is a protein or a fragment thereof having at least 8 amino acids, said protein or fragment being added to the culture medium, in a concentration of from 0.01 to 1000 μM.

12. The method according to claim 2, wherein said immature dendritic cells (DCs) are **loaded** with a DNA or RNA molecule which codes for said antigen.

13. The method according to claim 2, wherein a protein fragment, cells or cell fragments or nucleic acid sequences serve as the antigen in said antigen-antibody complex, and the antibody is one of class IgG or IgE.

14. The method according to claim 1, wherein said immature dendritic cells (DCs), prior to being frozen are contacted with a molecule which is capable of inhibiting apoptosis.

15. The method according to claim 1, wherein more than 75% of the mature dendritic cells (DCs), based on the number of frozen mature dendritic cells (DCs), have survived after said freezing and rethawing of the mature dendritic cells (DCs).

16. The method according to claim 1, wherein said method is suitable for the preparation of a vaccine from mature cryoconserved dendritic cells (DCs).

17. A method for finding advantageous conditions for the freezing of mature dendritic cells (DCs), comprising the method of: (a) providing immature DCs; (b) performing different cultures with immature DCs in the presence of different maturing stimulants; (c) culturing the DCs in medium with or without cytokines; (d) determining the fraction of living cells after at least 1 day of culture in said medium with or without cytokines; and (e) establishing that maturing stimulant which gave the highest survival rate.

18. The method according to claim 17, wherein the fraction of living cells is determined after at least 2 days culture in the medium with or without cytokines.

19. Frozen mature antigen-**loaded** dendritic cells.

20. Frozen mature antigen-**loaded** dendritic cells obtained by the method according to claim 1.

21. A vaccine comprising dendritic cells according to claim 19.

22. The method according to claim 1, wherein said immature dendritic cells (DCs) are prepared from CD34+ cells.

23. The method according to claim 1, wherein said immature dendritic cells (DCs) are isolated directly from blood.

24. The method according to claim 1, wherein said immature dendritic cells (DCs) or their precursor cells are obtained from leucapheresates.

25. The method according to claim 1, wherein said immature dendritic cells (DCs) or their precursor cells are obtained from fresh blood or bone marrow.

26. The method according to claim 4, wherein said IL-1 is IL-1β.

27. The method according to claim 4, wherein said prostaglandin is prostaglandin E2 (PGE2).

28. The method according to claim 4, wherein said lipopolysaccharide is monophosphoryl lipid A.

29. The method according to claim 4, wherein said bacterial cell product is lipoteichoic acid.

30. The method according to claim 4, wherein said nucleotide is adenosine triphosphate (ATP).

31. The method according to claim 4, wherein said double-stranded RNA is poly-I:C.

32. The method according to claim 1, wherein said culture medium comprises IL-1, IL-6, prostaglandin E2 (PGE2), and TNFα.

33. The method according to claim 1, wherein said maturing cocktail comprises **monocyte**-conditioned medium.

34. The method according to claim 33, wherein said maturing cocktail further comprises prostaglandin E2 (PGE2).

35. The method according to claim 7, wherein the culturing is performed for at least 6 hours.

36. The method according to claim 7, further comprising replacing the maturing cocktail of the culture medium during the culturing with fresh maturing cocktail.

37. The method according to claim 7, further comprising adding additional maturing stimulants to the culture medium during the culturing.

38. The method according to claim 7, wherein the culture medium further comprises an immune or maturing modulator.

39. The method according to claim 38, wherein the immune or maturing modulator is selected from the group consisting of IL-10, fumaric acid and esters thereof, mycophenolate mofetil, vitamin D3, and combinations thereof.

40. The method according to claim 8, wherein said one or more cryoprotectants are selected from the group consisting of DMSO, glycerol, polyvinylpyrrolidone, polyethylene glycol, albumin, choline chloride, amino acids, methanol, acetamide, glycerol monoacetate, and inorganic salts and combinations thereof.

41. The method according to claim 40, wherein said cryoprotectant is DMSO.

42. The method according to claim 8, wherein the one or more polyol compounds are selected from the group consisting of glucose, dextrane, sucrose, ethylene glycol, erythritol, D-ribitol, D-mannitol, D-sorbitol, inositol, and D-lactose.

43. The method according to claim 42, wherein said polyol compound is glucose.

44. The method according to claim 8, wherein said non-heterologous serum component is selected from the group consisting of autologous serum,

autologous plasma, allogenic serum, and allogenic plasma.

45. The method according to claim 8, wherein the non-heterologous serum component is selected from the group consisting of human serum albumin, autologous serum, allogenic human serum, and pool serum.

46. The method according to claim 11, wherein the culture medium comprises interleukin 1β (IL-1β), interleukin 6 (IL-6), prostaglandin E2 (PGE2), and tumor necrosis factor α (TNFα).

47. The method according to claim 14, wherein the molecule capable of inhibiting apoptosis is selected from the group consisting of CD40 ligand, TRANCE, and RANKL.

48. The method according to claim 15, wherein more than 85% of the immature dendritic cells (DCs) survive freezing and rethawing.

49. The method according to claim 17, wherein the culturing is in a medium comprising a cytokine.

50. The method according to claim 18, wherein the fraction of living cells is determined after at least 3 days of culturing.

51. The method according to claim 1, further comprising: (d) rethawing the frozen mature dendritic cells (DCs); and (e) loading the rethawed mature dendritic cells (DCs) with an antigen or antigen-antibody complex.

52. The method according to claim 51, wherein said mature dendritic cells (DCs) are **loaded** with a nucleic acid molecule that encodes said antigen, the nucleic acid molecule being selected from the group consisting of a DNA molecule and an RNA molecule.

53. The method according to claim 51, wherein: (a) the antigen is selected from the group consisting of a protein fragment, a cell, a cell fragment, and a nucleic acid sequence; and (b) the antibody is of a class selected from IgG and IgE.

54. The method according to claim 1, further comprising: (d) rethawing the frozen mature dendritic cells (DCs); and (e) contacting the rethawed matured dendritic cells (DCs) with a molecule that is capable of inhibiting apoptosis.

55. The method of claim 17, wherein the culturing of the dendritic cells (DCs) in step (c) is performed in a medium without cytokines.

56. The method of claim 17, wherein the culturing of the dendritic cells (DCs) in step (c) is performed in a medium comprising at least one cytokine.

57. The method of claim 1, wherein said mature dendritic cells (DCs) are **loaded** with an antigen or antigen-antibody complex prior to being frozen.

58. The method according to claim 57, wherein said antigen is a protein or a fragment thereof having at least 8 amino acids, said protein or fragment being added to the culture medium in a concentration of from 0.01 to 1000 μM.

59. The method according to claim 57, wherein said mature dendritic cells (DCs) are **loaded** with a DNA or RNA molecule which codes for said

antigen.

L26 ANSWER 29 OF 54 USPATFULL on STN
2004:306479 New isolated dendritic cells, a process for preparing the same and their use in pharmaceutical compositions.
Nardin, Alessandra, Paris, FRANCE
Kaiser, Andrew, St Andre Les, FRANCE
Boccaccio, Claire, Paris, FRANCE
Jacod, Sylvie, Bry Sur Marne, FRANCE
Abastado, Jean-Pierre, Paris, FRANCE
US 2004241147 A1 20041202
APPLICATION: US 2004-484382 A1 20040601 (10)
WO 2002-EP5411 20020516
PRIORITY: EP 2001-402010 20010725
DOCUMENT TYPE: Utility; APPLICATION.
CLM What is claimed is:

1. Dendritic cells irreversibly triggered to maturation, which are CD14 positive, which express MHC class I with a median fluorescence intensity less than about 1500 and CD86 with a median fluorescence intensity less than about 500, as determined by immunofluorescence staining and flow cytometry analysis.

2. Dendritic cells according to claim 1 which secrete less than about 3000 pg/ml of IL-12p70 and less than about 500 pg/ml of IL-10, as determined by Elisa assay for 106 cells/ml.

3. Dendritic cells according to claim 1, which express MHC class I with a median fluorescence intensity less than about 700 and CD86 with a median fluorescence intensity less than about 300, as determined by immunofluorescence staining and flow cytometry analysis, and which secrete less than about 80 pg/ml of IL-12p70 and less than about 300 pg/ml of IL-10, as determined by Elisa assay for 106 cells/ml.

4. Dendritic cells according to claim 1, which are CD83 negative.

5. Dendritic cells according to claim 3, presenting the following characteristics: CD83 expression with a median fluorescence intensity from about 3 to about 20 CD 14 expression with a median fluorescence intensity from about 20 to about 100 MHC Class I expression with a median fluorescence intensity from about 400 to about 700 CD86 expression with a median fluorescence intensity from about 100 to about 300 as determined by immunofluorescence staining and flow cytometry analysis, and: IL-12p70 secretion of 1 to about 80 pg/ml IL-10 secretion of about 15 to about 300 pg/ml. as determined by ELISA assay, for a total of 106 cells/ml.

6. Dendritic cells according to claim 1 which originate from immature dendritic cells derived from blood **monocytes** cultured for 1 to 16 hours, preferably 6 hours.

7. Dendritic cells according to claim 1, which have the properties that they can be arrested in their maturation process, and to resume maturation after this arrest when cultivated in appropriate conditions.

8. Dendritic cells according to claim 1 which have the properties of becoming mature in vitro in a culture medium containing no maturating factors and no cytokines, for a sufficient culture time.

9. Dendritic cells according to claim 1, which have the properties of becoming mature in vivo after injection to a patient.

10. Dendritic cells according to claim 1, which have been **loaded** with a drug, a nucleic acid or an antigen of interest, for example a tumoral antigen.

11. Dendritic cells according to claim 10 which have been **loaded** with lysates of tumor cells, in particular melanoma tumor cell lines.

12. Dendritic cells according to claim 1, which promote the development of T helper CD4+ T cells, and which activate cytotoxic CD8+ T lymphocytes specific for an antigen, after previous contact between said antigen and **phagocyting** dendritic cells.

13. Composition of dendritic cells according to claim 1, under frozen form in an appropriate cryopreservative medium.

14. Process for obtaining dendritic cells irreversibly triggered to maturation, which are CD14 positive, which express MHC class I with a median fluorescence intensity inferior to about 1500 and CD86 with a median fluorescence intensity inferior to about 500, as determined by immunofluorescence staining and flow cytometry analysis, comprising a step of contacting immature dendritic cells derived from blood **monocytes** and incubating them for 1 to 16 hours, preferably 6 h, with a combination of two factors: a--Cytokine or agonist of cytokine or cytokine inducing factor, and b--Bacterial mixture of membrane fractions and/or ribosomal fractions, or ligand or an agonist, said ligand or its agonist being different from a cytokine.

15. Process according to claim 14 for obtaining dendritic cells irreversibly triggered to maturation, which express MHC class I with a median fluorescence intensity inferior to about 700 and CD86 with a median fluorescence intensity inferior to about 300, as determined by immunofluorescence staining and flow cytometry analysis, and which secrete less than about 80 pg/ml of IL-12p70 and less than about 300 pg/ml of IL-10 as determined by Elisa assay for 106 cells/ml.

16. Process according to claim 14 where obtained dendritic cells are CD83 negative.

17. Process according to claim 14, wherein the cytokine is IFNγ, or wherein the cytokine inducing factor is poly I:C.

18. Process according to claim 14 wherein the bacterial mixture of membrane fractions and/or ribosomal fractions is a membrane subtraction of one strain of bacteria.

19. Process according to claim 18 wherein the membrane subfraction is a purified protein obtained from said membrane subfraction.

20. Process according to claim 18, wherein the bacterial mixture of membrane and/or ribosomal fractions is RibomunylR, and the membrane subtraction is FMKp (Klebsiella pneumoniae membrane fraction).

21. Process according to claim 14, wherein the cytokine is IFNγ and the membrane subfraction is FMKp.

22. Process according to claim 21 wherein the used concentration of IFNγ is about 500 U/ml and the used concentration of FMKp is about 1 µg/ml.

23. Process according to claim 14, wherein the ligand is an antibody anti CD40 or a CD40 ligand.

24. Process according to claim 14, wherein the ligand is an inducible Heat shock protein 70 or isolated polypeptide sequences from it.

25. Dendritic cells irreversibly triggered to maturation such as obtained by the process according to claim 14.

26. Mature dendritic cells which have a secretion of IL-12p70 higher than secretion of IL-10.

27. Mature dendritic cells which secrete more than about 1000 pg/ml of IL-12p70 and less than about 100 pg/ml of IL-10 (as determined by Elisa assay for 106 cells/ml) for at least 24 hours, and stimulate Th1 and cytotoxic immune response.

28. Process for preparing mature dendritic cells from irreversibly triggered dendritic cells according to claim 1, which comprises a step of culture of said irreversibly triggered dendritic cells without exogenous maturation factor nor cytokine added, in vitro or in vivo.

29. Mature dendritic cells such as obtained by the process according to claim 27.

30. Pharmaceutical composition containing as active substance dendritic cells irreversibly triggered to maturation, according to claim 1, having interiorised antigens, preferably vaccinal antigens, in association with a pharmaceutically acceptable vehicle.

31. Cellular vaccine composition containing as active substance dendritic cells irreversibly triggered to maturation according to claim 1, in a amount of about 104 to about 109, and preferably about 105 to about 107 of said cells per vaccinal dose.

L26 ANSWER 30 OF 54 USPATFULL on STN
2004:279868 Method for generating highly active human dendritic cells from monocytes.
Belardelli, Filippo, Roma, ITALY
Santini, Stefano Maria, Roma, ITALY
Parlato, Stefania, Roma, ITALY
Di Pucchio, Tiziana, Lungo, ITALY
Logozzi, Mariantonia, Roma, ITALY
Lapenta, Caterina, Firenze, ITALY
Ferrantini, Maria, Roma, ITALY
Santodanato, Laura, Roma, ITALY
D'Agostino, Giuseppina, Roma, ITALY
US 2004219168 A1 20041104
APPLICATION: US 2004-475704 A1 20040506 (10)
WO 2002-EP4709 20020429
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A process for the preparation of dendritic cells comprising the step of culturing mononuclear cells in a culture medium containing type I interferon, wherein said mononuclear cells are chosen from the group consisting of total peripheral blood mononuclear cells, adherent peripheral blood mononuclear cells and highly purified CD14+ **monocytes** isolated from peripheral blood mononuclear cells.

2. A process according to claim 1, wherein said dendritic cells are obtained in no more than three days.

3. A process according to claim 1, wherein said type I interferon is

chosen from the group consisting of natural or recombinant IFN.quadrature., natural or recombinant INFO consensus interferon and any synthetic type I interferon.

4. A process according to claim 1, wherein the concentration of said type I interferon in the culture medium is greater than 100 IU/ml.

5. A process according to claim 4 wherein said concentration is between 100 and 10.000 IU/ml.

6. A process according to claim 5 wherein said concentration is between 400 and 10.000 IU/ml.

7. A process according to claim 6 wherein said concentration is between 500 and 2.000 IU/ml.

8. A process according to claim 7 wherein said concentration is about 1000 IU/ml.

9. A process according to claim 1 wherein said culture medium also contains a cell growth factor.

10. A process according to claim 9 wherein said cell growth factor is GM-CSF.

11. A process according to claim 10 wherein said the concentration of said GM-CSF in the medium is between 250 and 1000 IU/ml.

12. A process according to claim 1 wherein said process further comprises the step of contacting the dendritic cells obtained with a maturation agent.

13. Dendritic cells obtainable with a process according to claim 1.

14. Dendritic cells according to claim 13 said cells having been **loaded** with antigenic peptides or proteins, with a cellular extract containing at least one antigen or with nucleic acid molecules encoding for antigens to which an immune response is of interest

15. Dendritic cells according to claim 13 wherein said cells are in a dehydrated or frozen form in an appropriate cryo-preservative medium.

16. A kit for preparing dendritic cells according to claim 13 comprising: a) single use elements necessary for the culture and the washing of the cells; b) a composition comprising type I IFN and compatible additives; c) optionally a composition comprising a cell growth factor and compatible additives; and d) optionally a composition comprising antigens or nucleic acids encoding for antigens to which an immune response is of interest.

17. A pharmaceutical composition or a vaccine comprising, as an adjuvant, the dendritic cells according to claim 13 together with at least one immunogen and a pharmaceutically acceptable vehicle or an auxiliary agent.

18. A pharmaceutical composition or a vaccine comprising, as an active principle, the dendritic cells according to claim 13 together with a pharmaceutically acceptable vehicle or auxiliary agent.

19. (cancelled)

20. Use of dendritic cells according to claim 13 for the preparation of

a vaccine or a pharmaceutical composition for the prevention or the treatment of a pathology associated with the presence of an antigen in the human body.

21. Use according to claim 20 wherein said pathology is an infectious or neoplastic disease.

22. Use according to claim 21 wherein said infectious disease is a viral infection.

23. Use according to claim 22 wherein said viral infection is a HIV, a HBV or a HCV infection.

24. Use according to claim 20 wherein said neoplastic disease is a lymphoma.

25. Use according to claim 21 wherein said neoplastic disease is virally induced.

26. Use according to claim 25 wherein said neoplastic disease is induced by Epstein-Barr virus.

27. Use according to claim 20 wherein said pharmaceutical composition is suitable for administration at the site of infection or within the tumour.

28. A method for the ex-vivo expansion of T cells, comprising the step of putting in contact said T cells with the dendritic cells according to claim 13.

29. (cancelled)

30. A pharmaceutical composition containing, as active principle, the T cells according to claim 28.

L26 ANSWER 31 OF 54 USPATFULL on STN
2004:246645 Treatment and prevention of reactive oxygen metabolite-mediated cellular damage.
Hellstrand, Kristoffer, Goteborg, SWEDEN
Hermodsson, Svante, Molndal, SWEDEN
Gehlsen, Kurt R., Encinitas, CA, UNITED STATES
US 2004191239 A1 20040930
APPLICATION: US 2004-819594 A1 20040407 (10)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A kit for the treatment of a condition caused or exacerbated by ROM-mediated damage, comprising: an infusion device; and a compound effective to inhibit the production or release of the ROMs, wherein the ROM production or release compound is selected from the group consisting of histamine, histamine phosphate, histamine dihydrochloride, and H2 receptor agonists.

2. The kit of claim 1, wherein the infusion device is adapted to administer the compound by a method selected from the group consisting of injection, implantation infusion device, inhalation, ingestion, diffusion and by suppository.

3. The kit of claim 1, wherein the infusion device is selected from the group consisting of pre-**loaded** syringes, syringe pumps, auto injector systems and minipumps.

4. The kit of claim 2, wherein the injection method is selected from the group consisting of subcutaneous injection, intramuscular injection and intravenous injection.

5. The kit of claim 2, wherein the diffusion method is selected from the group consisting of transdermal diffusion and transmucosal diffusion.

6. The kit of claim 1, further comprising an effective amount of a ROM scavenger.

7. The kit of claim 6, wherein the ROM scavenger is selected from the group consisting of catalase, glutathione peroxidase, ascorbate peroxidase, superoxide dismutase, glutathione peroxidase, ascorbate peroxidase, vitamin A, vitamin E, and vitamin C.

8. The kit of claim 6, wherein the infusion device is adapted to administer the compound by a method selected from the group consisting of injection, implantation infusion device, inhalation, ingestion, diffusion and by suppository.

9. The kit of claim 1, further comprising an analgesic, an anesthetic or an anxiolytic compound.

10. The kit of claim 1, further comprising IL-3, a retinoid, an allergen, a 5HT agonist, serotonin, and diphenyleneiodonium.

11. The kit of claim 1, wherein said condition is radiation injury.

12. A pre-**loaded** delivery device, comprising a compound effective to inhibit the production or release of the ROMs, wherein the ROM production or release compound is selected from the group consisting of histamine, histamine phosphate, histamine dihydrochloride, and H2 receptor agonists, and a compound effective for the scavenging of ROMs.

13. The pre-**loaded** delivery device of claim 12, wherein said delivery device is a syringe.

14. The pre-**loaded** delivery device of claim 12, wherein said compound effective for the scavenging of ROMs is selected from the group consisting of catalase, glutathione peroxidase, ascorbate peroxidase, superoxide dismutase, glutathione peroxidase, ascorbate peroxidase, vitamin A, vitamin E, and vitamin C.

15. The pre-**loaded** delivery device of claim 12, wherein said device comprises 0.4 mg to 10 mg of histamine.

16. The pre-**loaded** delivery device of claim 12, wherein said device comprises 0.1 to 10 mg of an enzymatic ROM scavenger.

17. The pre-**loaded** delivery device of claim 12, wherein said device comprises 1.0 picogram to 1 mg of a mineral non-enzymatic ROM scavenger.

18. The pre-**loaded** delivery device of claim 12, wherein said composition comprises 1 to 5000 IU of a non-enzymatic ROM scavenger selected from the group consisting of vitamin A and vitamin E.

19. A method for treating a subject suffering from radiation injury, comprising: identifying a subject presenting the symptoms of radiation injury caused or exacerbated by release of reactive oxygen metabolites ("ROMs") from **phagocytic** cells resulting in ROM-mediated oxidative damage; and administering a compound effective to inhibit the

production or release of the ROMs and a compound effective for the scavenging of ROMs with the pre-**loaded** delivery device of claim 12.

L26 ANSWER 32 OF 54 USPATFULL on STN
2004:233312 Methods for predicting the predisposition of an individual to total joint replacement failure.
Boynton, Erin Lynn, Toronto, CANADA
US 2004180383 A1 20040916
APPLICATION: US 2003-718601 A1 20031124 (10)
PRIORITY: US 2002-428718P 20021125 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A method for assessing a patient for predisposition to total joint replacement failure, comprising the steps of: a) assaying a patient sample containing **monocytes/macrophages** by measuring the level at which at least one pro-inflammatory marker is produced in response to incubation with a fixed or varied volume of a particulate form of the joint replacement material; b) comparing that measured level with either (i) a first reference level established for a population of primary patients or (ii) a second reference level established for a population of revision patients; and c) wherein a patient is identified as having a predisposition to total joint replacement if (a) the measured level is at least twice the first reference level, or (b) if the measured level is statistically no different from the second reference level, or (c) if the level when measured at said varied particulate volume is characterized by a bell-shaped dose response curve.

2. The method according to claim 1, wherein said levels using said varied volume of the particulate form of the joint replacement material to produce a dose response curve, and identifying patients predisposed to joint replacement failure as those patients for which a bell-shaped dose response curve is generated.

3. The method according to claim 1, wherein the particulate joint material is polyethylene.

4. The method according to claim 1, wherein the pro-inflammatory marker is selected from a cytokine and an enzyme.

5. The method according to claim 4, wherein the pro-inflammatory marker is selected from interleukin-6, interleukin-1B and tumour necrosis factor alpha.

6. The method according to claim 4, wherein the enzyme is TRAP.

7. The method according to claim 1, in which the levels of at least two pro-inflammatory markers are correlated, and compared with said reference levels to identify patients having said predisposition.

8. The method according to claim 1, wherein the level at which the pro-inflammatory marker is produced is measured by detecting the secreted form of that marker.

9. The method according to claim 1, wherein the level at which the pro-inflammatory marker is produced is measured by detecting transcripts of a gene encoding said marker.

10. A kit comprising one or more reagents for performing the assay defined according to any preceding claim, and instructions for assessing

said predisposition based on the results of said assay.

11. A kit according to claim 10, comprising an assay substrate pre-**loaded** with particulate joint replacement material.

12. A kit according to claim 11, wherein said substrate comprises particulate joint replacement material pre-**loaded** with particulates in a range of different volumes.

L26 ANSWER 33 OF 54 USPATFULL on STN
2004:202969 Yeast-based vaccines as immunotherapy.
Franzusoff, Alex, Denver, CO, UNITED STATES
Bellgrau, Donald, Denver, CO, UNITED STATES
US 2004156858 A1 20040812
APPLICATION: US 2003-738646 A1 20031216 (10)
PRIORITY: US 2002-434163P 20021216 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A method to protect an animal against a cancer, comprising administering to an animal that has or is at risk of developing a cancer, a vaccine to reduce or prevent at least one symptom of the cancer in the animal, wherein the vaccine comprises: a) a yeast vehicle; and b) a fusion protein expressed by the yeast vehicle, the fusion protein comprising: i) at least one cancer antigen; and ii) a peptide linked to the N-terminus of the cancer antigen, the peptide consisting of at least two amino acid residues that are heterologous to the cancer antigen, wherein the peptide stabilizes the expression of the fusion protein in the yeast vehicle or prevents posttranslational modification of the expressed fusion protein; wherein the amino acid residue at position one of the fusion protein is a methionine; wherein the amino acid residue at position two of the fusion protein is not a glycine or a proline; wherein none of the amino acid residues at positions 2-6 of the fusion protein is a methionine; and, wherein none of the amino acid residues at positions 2-5 of the fusion protein is a lysine or an arginine.

2. The method of claim 1, wherein the peptide consists of at least 2-6 amino acid residues that are heterologous to the cancer antigen.

3. The method of claim 1, wherein the peptide comprises an amino acid sequence of M-X_2--X_3--X_4--X_5--X_6; wherein
X_2 is any amino acid except glycine, proline, lysine or arginine;
wherein X_3 is any amino acid except methionine, lysine or arginine;
wherein X_4 is any amino acid except methionine, lysine or arginine;
wherein X_5 is any amino acid except methionine, lysine or arginine;
and wherein X_6 is any amino acid except methionine.

4. The method of claim 3, wherein X_6 is a proline.

5. The method of claim 1, wherein the peptide comprises an amino acid sequence of M-A-D-E-A-P (SEQ ID NO: 1).

6. A method to protect an animal against a cancer, comprising administering to an animal that has or is at risk of developing a cancer, a vaccine to reduce or prevent at least one symptom of the cancer in the animal, wherein the vaccine comprises: a) a yeast vehicle; and b) a fusion protein expressed by the yeast vehicle, the fusion protein comprising: i) at least one cancer antigen; and ii) a yeast protein linked to the N-terminus of the cancer antigen, wherein the yeast protein consists of between about two and about 200 amino

acids of an endogenous yeast protein, wherein the yeast protein stabilizes the expression of the fusion protein in the yeast vehicle or prevents posttranslational modification of the expressed fusion protein.

7. The method of claim 6, wherein the yeast protein comprises an antibody epitope for identification and purification of the fusion protein.

8. The method of claim 1 or claim 6, wherein the fusion protein comprises at least two or more cancer antigens.

9. The method of claim 1 or claim 6, wherein the fusion protein comprises at least one or more immunogenic domain of one or more cancer antigens.

10. The method of claim 1 or claim 6, wherein the cancer antigen is an antigen associated with a cancer selected from the group consisting of: melanomas, squamous cell carcinoma, breast cancers, head and neck carcinomas, thyroid carcinomas, soft tissue sarcomas, bone sarcomas, testicular cancers, prostatic cancers, ovarian cancers, bladder cancers, skin cancers, brain cancers, angiosarcomas, hemangiosarcomas, mast cell tumors, primary hepatic cancers, lung cancers, pancreatic cancers, gastrointestinal cancers, renal cell carcinomas, hematopoietic neoplasias and metastatic cancers thereof.

11. The method of claim 1 or claim 6, wherein the cancer antigen is wild-type or mutant protein encoded by a ras gene.

12. The method of claim 11, wherein the cancer antigen is wild-type or mutant protein encoded by a ras gene selected from the group consisting of: K-ras, N-ras and H-ras genes.

13. The method of claim 11, wherein the ras gene encodes a Ras protein with single or multiple mutations.

14. The method of claim 1 or claim 6, wherein the cancer antigen comprises fragments of at least 5-9 contiguous amino acid residues of a wild-type Ras protein containing amino acid positions 12, 13, 59 or 61 relative to the wild-type Ras protein, wherein the amino acid residues at positions 12, 13, 59 or 61 are mutated with respect to the wild-type Ras protein.

15. The method of claim 1 or claim 6, wherein the cancer antigen consists of a fusion protein construct comprising multiple domains, wherein each domain consists of a peptide from an oncoprotein, the peptide consisting of at least 4 amino acid residues flanking either side of and including a mutated amino acid that is found in the protein, wherein the mutation is associated with tumorigenicity.

16. The method of claim 15, wherein the fusion protein construct consists of at least one peptide that is fused in frame with another mutated tumor antigen, wherein the peptide is selected from the group consisting of: a) a peptide comprising at least from positions 8-16 of SEQ ID NO:3, wherein the amino acid residue at position 12 with respect to SEQ ID NO:3 is mutated as compared to SEQ ID NO:3; b) a peptide comprising at least from positions 9-17 of SEQ ID NO:3, wherein the amino acid residue at position 13 with respect to SEQ ID NO:3 is mutated as compared to SEQ ID NO:3; c) a peptide comprising at least from positions 55-63 of SEQ ID NO:3, wherein the amino acid residue at position 59 with respect to SEQ ID NO:3 is mutated as compared to SEQ ID NO:3; and d) a peptide comprising at least from positions 57-65 of SEQ ID NO:3, wherein the amino acid residue at position 61 with respect to

SEQ ID NO:3 is mutated as compared to SEQ ID NO:3.

17. The method of claim 16, wherein the mutated tumor antigen is a Ras protein comprising at least one mutation relative to a wild-type Ras protein sequence.

18. The method of claim 1 or claim 6, wherein the yeast vehicle is selected from the group consisting of a whole yeast, a yeast spheroplast, a yeast cytoplast, a yeast ghost, and a subcellular yeast membrane extract or fraction thereof.

19. The method of claim 1 or claim 6, wherein a yeast cell or yeast spheroplast used to prepare the yeast vehicle was transformed with a recombinant nucleic acid molecule encoding the cancer antigen such that the cancer antigen is recombinantly expressed by the yeast cell or yeast spheroplast.

20. The method of claim 19, wherein the yeast cell or yeast spheroplast that recombinantly expresses the cancer antigen is used to produce a yeast vehicle comprising a yeast cytoplast, a yeast ghost, or a subcellular yeast membrane extract or fraction thereof.

21. The method of claim 1 or claim 6, wherein the yeast vehicle is from a non-pathogenic yeast.

22. The method of claim 1 or claim 6, wherein the yeast vehicle is from a yeast selected from the group consisting of: Saccharomyces, Schizosaccharomyces, Kluveromyces, Hansenula, Candida and Pichia.

23. The method of claim 1 or claim 6, wherein Saccharomyces is S. cerevisiae.

24. The method of claim 1 or claim 6, wherein the vaccine is administered to the respiratory tract.

25. The method of claim 1 or claim 6, wherein the vaccine is administered by a parenteral route of administration.

26. The method of claim 1 or claim 6, wherein the vaccine further comprises dendritic cells or **macrophages**, wherein the yeast vehicle expressing the fusion protein is delivered to dendritic cells or **macrophages** ex vivo and wherein the dendritic cell or **macrophage** containing the yeast vehicle expressing the cancer antigen is administered to the animal.

27. The method of claim 26, wherein the dendritic cell or the yeast vehicle has been additionally **loaded** with free antigen.

28. The method of claim 1 or claim 6, wherein the vaccine is administered as a therapeutic vaccine.

29. The method of claim 1 or claim 6, wherein the vaccine is administered as a prophylactic vaccine.

30. The method of claim 1 or claim 6, wherein the animal has or is at risk of developing a cancer selected from the group consisting of brain cancer, lung cancer, breast cancer, melanoma, and renal cancer.

31. The method of claim 1 or claim 6, wherein the animal has cancer and wherein administration of the vaccine occurs after surgical resection of a tumor from the animal.

32. The method of claim 1 or claim 6, wherein the animal has cancer and wherein administration of the vaccine occurs after surgical resection of a tumor from the animal and after administration of non-myeloablative allogeneic stem cell transplantation.

33. The method of claim 1 or claim 6, wherein the animal has cancer and wherein administration of the vaccine occurs after surgical resection of a tumor from the animal, after administration of non-myeloablative allogeneic stem cell transplantation, and after allogeneic donor lymphocyte infusion.

34. A method to protect an animal against a brain cancer or a lung cancer, comprising administering to the respiratory tract of an animal that has or is at risk of developing a brain cancer or a lung cancer, a vaccine comprising a yeast vehicle and at least one cancer antigen, to reduce or prevent at least one symptom of the brain cancer or lung cancer in the animal.

35. The method of claim 34, wherein the vaccine comprises at least two or more cancer antigens.

36. The method of claim 34, wherein the cancer antigen is a fusion protein comprising at least one or more cancer antigens.

37. The method of claim 34, wherein the cancer antigen is a fusion protein comprising at least one or more immunogenic domains of one or more cancer antigens.

38. The method of claim 34, wherein the cancer antigen consists of a fusion protein construct comprising multiple domains, wherein each domain consists of a peptide from an oncoprotein, the peptide consisting of at least 4 amino acid residues flanking either side of and including a mutated amino acid that can be found in the protein, wherein the mutation is associated with tumorigenicity.

39. The method of claim 34, wherein the yeast vehicle expresses the cancer antigen, and wherein the cancer antigen is a fusion protein comprising: a) at least one cancer antigen; and b) a peptide linked to the N-terminus of the cancer antigen, the peptide consisting of at least two amino acid residues that are heterologous to the cancer antigen, wherein the peptide stabilizes the expression of the fusion protein in the yeast vehicle or prevents posttranslational modification of the expressed fusion protein; wherein the amino acid residue at position one of the fusion protein is a methionine; wherein the amino acid residue at position two of the fusion protein is not a glycine or a proline; wherein none of the amino acid residues at positions 2-6 of the fusion protein is a methionine; and, wherein none of the amino acid residues at positions 2-5 of the fusion protein is a lysine or an arginine.

40. The method of claim 34, wherein the yeast vehicle expresses the cancer antigen, and wherein the cancer antigen is a fusion protein comprising: a) at least one cancer antigen; and b) a yeast protein linked to the N-terminus of the cancer antigen, wherein the yeast protein consists of between about two and about 200 amino acids of an endogenous yeast protein, wherein the yeast protein stabilizes the expression of the fusion protein in the yeast vehicle or prevents posttranslational modification of the expressed fusion protein.

41. The method of claim 34, wherein the yeast vehicle is selected from the group consisting of a whole yeast, a yeast spheroplast, a yeast cytoplast, a yeast ghost, and a subcellular yeast membrane extract or

fraction thereof.

42. The method of claim 34, wherein a yeast cell or yeast spheroplast used to prepare the yeast vehicle was transformed with a recombinant nucleic acid molecule encoding the cancer antigen such that the cancer antigen is recombinantly expressed by the yeast cell or yeast spheroplast.

43. The method of claim 42, wherein the yeast cell or yeast spheroplast that recombinantly expresses the cancer antigen is used to produce a yeast vehicle comprising a yeast cytoplast, a yeast ghost, or a subcellular yeast membrane extract or fraction thereof.

44. The method of claim 34, wherein the yeast vehicle was **loaded** intracellularly with the cancer antigen.

45. The method of claim 34, wherein the cancer antigen was covalently or non-covalently attached to the yeast vehicle.

46. The method of claim 34, wherein the yeast vehicle and the cancer antigen were associated by mixing.

47. The method of claim 34, wherein the vaccine is administered by intranasal administration.

48. The method of claim 34, wherein the vaccine is administered by intratracheal administration.

49. The method of claim 34, wherein the yeast vehicle and the cancer antigen are delivered to dendritic cells or **macrophages** ex vivo and wherein the dendritic cell or **macrophage** containing the yeast vehicle and cancer antigen are administered to the respiratory tract of the animal.

50. The method of claim 34, wherein the method protects the animal against a brain cancer.

51. The method of claim 50, wherein the brain cancer is a primary brain cancer.

52. The method of claim 50, wherein the brain cancer is a glioblastoma multiforme.

53. The method of claim 50, wherein the brain cancer is a metastatic cancer from a different organ.

54. The method of claim 34, wherein the method protects the animal against a lung cancer.

55. The method of claim 54, wherein the lung cancer is a primary lung cancer.

56. The method of claim 54, wherein the lung cancer is selected from the group consisting of non-small cell carcinomas, small cell carcinomas and adenocarcinomas.

57. The method of claim 54, wherein the lung cancer is a metastatic cancer from a different organ.

58. The method of claim 34, wherein the vaccine is administered as a therapeutic vaccine.

59. The method of claim 34, wherein the vaccine is administered as a prophylactic vaccine.

60. The method of claim 34, wherein the yeast vehicle is from a non-pathogenic yeast.

61. The method of claim 34, wherein the yeast vehicle is from a yeast selected from the group consisting of: Saccharomyces, Schizosaccharomyces, Kluveromyces, Hansenula, Candida and Pichia.

62. The method of claim 34, wherein Saccharomyces is S. cerevisiae.

63. A method to elicit an antigen-specific humoral immune response and an antigen-specific cell-mediated immune response in an animal, the method comprising administering to the animal a therapeutic composition comprising: a) a yeast vehicle; and b) a fusion protein expressed by the yeast vehicle, the fusion protein comprising: i) at least one antigen; and ii) a peptide linked to the N-terminus of the antigen, the peptide consisting of at least two amino acid residues that are heterologous to the antigen, wherein the peptide stabilizes the expression of the fusion protein in the yeast vehicle or prevents posttranslational modification of the expressed fusion protein; wherein the amino acid residue at position one of the fusion protein is a methionine; wherein the amino acid residue at position two of the fusion protein is not a glycine or a proline; wherein none of the amino acid residues at positions 2-6 of the fusion protein is a methionine; and, wherein none of the amino acid residues at positions 2-5 of the fusion protein is a lysine or an arginine.

64. The method of claim 63, wherein the peptide consists of at least six amino acid residues that are heterologous to the antigen.

65. The method of claim 63, wherein the peptide comprises an amino acid sequence of M-X_2--X_3--X_4--X_5--X_6; wherein
X_2 is any amino acid except glycine, proline, lysine or arginine;
wherein X_3 is any amino acid except methionine, lysine or arginine;
wherein X_4 is any amino acid except methionine, lysine or arginine;
wherein X_5 is any amino acid except methionine, lysine or arginine;
and wherein X_6 is any amino acid except methionine.

66. The method of claim 65, wherein X_6 is a proline.

67. The method of claim 63, wherein the peptide comprises an amino acid sequence of M-A-D-E-A-P (SEQ ID NO:1).

68. The method of claim 63, wherein the antigen is selected from the group consisting of: a viral antigen, an overexpressed mammalian cell surface molecule, a bacterial antigen, a fungal antigen, a protozoan antigen, a helminth antigen, an ectoparasite antigen, a cancer antigen, a mammalian cell molecule harboring one or more mutated amino acids, a protein normally expressed pre- or neo-natally by mammalian cells, a protein whose expression is induced by insertion of an epidemiologic agent (e.g. virus), a protein whose expression is induced by gene translocation, and a protein whose expression is induced by mutation of regulatory sequences.

69. A method to elicit an antigen-specific humoral immune response and an antigen-specific cell-mediated immune response in an animal, the method comprising administering to the animal a therapeutic composition comprising: a) a yeast vehicle; and b) a fusion protein expressed by the yeast vehicle, the fusion protein comprising: i) at least one antigen; and ii) a yeast protein linked to the N-terminus of the

antigen, wherein the yeast protein consists of between about two and about 200 amino acids of an endogenous yeast protein, wherein the yeast protein stabilizes the expression of the fusion protein in the yeast vehicle or prevents posttranslational modification of the expressed fusion protein.

70. The method of claim 69, wherein the yeast protein comprises an antibody epitope for identification and purification of the fusion protein.

71. A vaccine comprising: a) a yeast vehicle; and b) a fusion protein expressed by the yeast vehicle, the fusion protein comprising: i) at least one antigen; and ii) a peptide linked to the N-terminus of the antigen, the peptide consisting of at least two amino acid residues that are heterologous to the antigen, wherein the peptide stabilizes the expression of the fusion protein in the yeast vehicle or prevents posttranslational modification of the expressed fusion protein; wherein the amino acid residue at position one of the fusion protein is a methionine; wherein the amino acid residue at position two of the fusion protein is not a glycine or a proline; wherein none of the amino acid residues at positions 2-6 of the fusion protein is a methionine; and, wherein none of the amino acid residues at positions 2-5 of the fusion protein is a lysine or an arginine.

72. The vaccine of claim 71, wherein the peptide consists of at least six amino acid residues that are heterologous to the antigen.

73. The vaccine of claim 71, wherein the peptide comprises an amino acid sequence of M-X2--X3--X4--X5--X6; wherein
X2 is any amino acid except glycine, proline, lysine or arginine;
wherein X3 is any amino acid except methionine, lysine or arginine;
wherein X4 is any amino acid except methionine, lysine or arginine;
wherein X5 is any amino acid except methionine, lysine or arginine;
and wherein X6 is any amino acid except methionine.

74. The vaccine of claim 73, wherein X6 is a proline.

75. The vaccine of claim 73, wherein the peptide comprises an amino acid sequence of M-A-D-E-A-P (SEQ ID NO: 1).

76. The vaccine of claim 73, wherein the antigen is selected from the group consisting of: a viral antigen, a mammalian cell surface molecule, a bacterial antigen, a fungal antigen, a protozoan antigen, a helminth antigen, an ectoparasite antigen, a cancer antigen, a mammalian cell molecule harboring one or more mutated amino acids, a protein normally expressed pre- or neo-natally by mammalian cells, a protein whose expression is induced by insertion of an epidemiologic agent (e.g. virus), a protein whose expression is induced by gene translocation, and a protein whose expression is induced by mutation of regulatory sequences.

77. The vaccine of claim 73, wherein the antigen is a cancer antigen.

78. A vaccine comprising: a) a yeast vehicle; and b) a fusion protein expressed by the yeast vehicle, the fusion protein comprising: i) at least one antigen; and ii) a yeast protein linked to the N-terminus of the antigen, wherein the yeast protein consists of between about two and about 200 amino acids of an endogenous yeast protein, wherein the yeast protein stabilizes the expression of the fusion protein in the yeast vehicle or prevents posttranslational modification of the expressed fusion protein.

79. The vaccine of claim 78, wherein the yeast protein comprises an antibody epitope for identification and purification of the fusion protein.

80. A method to treat a patient that has cancer, comprising: a) treating a patient that has cancer by nonmyeloablative stem cell transfer effective to establish a stable mixed bone marrow chimerism, wherein the stem cells are provided by an allogeneic donor; b) administering lymphocytes obtained from the allogeneic donor to the patient; and c) administering to the patient, after step (b), a vaccine comprising a yeast vehicle and at least one cancer antigen.

81. The method of claim 80, further comprising administering to the allogeneic donor, prior to step (a), a vaccine comprising a yeast vehicle and at least one cancer antigen.

82. The method of claim 80, further comprising removing a tumor from the patient prior to performing step (a).

83. The method of claim 80 wherein the vaccine comprises at least two or more cancer antigens.

84. The method of claim 80, wherein the cancer antigen is a fusion protein comprising one or more cancer antigens.

85. The method of claim 80, wherein the cancer antigen is a fusion protein comprising one or more immunogenic domains of one or more cancer antigens.

86. The method of claim 80, wherein the cancer antigen consists of a fusion protein construct comprising multiple domains, wherein each domain consists of a peptide from an oncoprotein, the peptide consisting of at least 4 amino acid residues flanking either side of and including a mutated amino acid that is found in the protein, wherein the mutation is associated with tumorigenicity.

87. The method of claim 80, wherein the yeast vehicle expresses the cancer antigen, and wherein the cancer antigen is a fusion protein comprising: a) at least one cancer antigen; and b) a peptide linked to the N-terminus of the cancer antigen, the peptide consisting of at least two amino acid residues that are heterologous to the cancer antigen, wherein the peptide stabilizes the expression of the fusion protein in the yeast vehicle or prevents posttranslational modification of the expressed fusion protein; wherein the amino acid residue at position one of the fusion protein is a methionine; wherein the amino acid residue at position two of the fusion protein is not a glycine or a proline; wherein none of the amino acid residues at positions 2-6 of the fusion protein is a methionine; and, wherein none of the amino acid residues at positions 2-5 of the fusion protein is a lysine or an arginine.

88. The method of claim 80, wherein the yeast vehicle expresses the cancer antigen, and wherein the cancer antigen is a fusion protein comprising: a) at least one cancer antigen; and b) a yeast protein linked to the N-terminus of the cancer antigen, wherein the yeast protein consists of between about two and about 200 amino acids of an endogenous yeast protein, wherein the yeast protein stabilizes the expression of the fusion protein in the yeast vehicle or prevents posttranslational modification of the expressed fusion protein.

89. The method of claim 80, wherein the yeast vehicle is selected from the group consisting of a whole yeast, a yeast spheroplast, a yeast

cytoplast, a yeast ghost, and a subcellular yeast membrane extract or fraction thereof.

90. The method of claim 80, wherein a yeast cell or yeast spheroplast used to prepare the yeast vehicle was transformed with a recombinant nucleic acid molecule encoding the cancer antigen such that the cancer antigen is recombinantly expressed by the yeast cell or yeast spheroplast.

91. The method of claim 90, wherein the yeast cell or yeast spheroplast that recombinantly expresses the cancer antigen is used to produce a yeast vehicle comprising a yeast cytoplast, a yeast ghost, or a subcellular yeast membrane extract or fraction thereof.

92. The method of claim 80, wherein the yeast vehicle was **loaded** intracellularly with the cancer antigen.

93. The method of claim 80, wherein the cancer antigen was covalently or non-covalently attached to the yeast vehicle.

94. The method of claim 80, wherein the yeast vehicle and the cancer antigen were associated by mixing.

95. The method of claim 80, wherein the vaccine is administered by intranasal administration.

96. The method of claim 80, wherein the vaccine is administered by parenteral administration.

97. The method of claim 80, wherein the yeast vehicle and the cancer antigen are delivered to dendritic cells or **macrophages** ex vivo and wherein the dendritic cell or **macrophage** containing the yeast vehicle and cancer antigen are administered to the respiratory tract of the animal.

98. The method of claim 80, wherein the yeast vehicle is from a non-pathogenic yeast.

99. The method of claim 80, wherein the yeast vehicle is from a yeast selected from the group consisting of: Saccharomyces, Schizosaccharomyces, Kluveromyces, Hansenula, Candida and Pichia.

100. The method of claim 80, wherein Saccharomyces is S. cerevisiae.

L26 ANSWER 34 OF 54 USPATFULL on STN
2004:174329 Methods for treating a patient undergoing chemotherapy.
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University of Southern California, Los Angeles, CA, United States (U.S. corporation)
US 6762167 B1 20040713
APPLICATION: US 2000-723197 20001127 (9)
PRIORITY: US 2000-243955P 20001027 (60)
US 2000-235040P 20000925 (60)
US 2000-233375P 20000918 (60)
US 2000-220804P 20000725 (60)
US 2000-201470P 20000503 (60)
US 1998-92633P 19980713 (60)
US 1998-84908P 19980511 (60)
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

CLM What is claimed is:

1. An improved method for chemotherapy in a human patient, wherein the improvement comprises administering to the human chemotherapy patient an amount of at least one active agent effective to treat chemotherapy side effects, or to reduce the frequency, severity, or the frequency and severity of chemotherapy side effects, wherein the active agent comprises a sequence consisting of at least five contiguous amino acids of groups R1-R8 in the sequence of general formula I
R1-R2-R3-R4-R5-R6-R7-R8 Wherein
R1 is Asp; R2 is Arg; R3 is Val; R4 is Tyr; R5
is Ile; R6 is His; R7 is Pro; and R8 is Phe or is absent,
excluding sequences including R4 as an N-terminal Tyr group; and wherein the active agent is not SEQ ID NO:1, wherein the chemotherapy side effects are selected from the group consisting of hematopoietic toxicity, decreased mobilization of hematopoietic progenitor cells from bone marrow into the peripheral blood, anemia, myelosuppression, pancytopenia, thrombocytopenia, neutropenia, lymphopenia, leukopenia, stomatitis, alopecia, headache, and muscle pain; and wherein said administering is for a time and under conditions effective to reduce the frequency, severity, or the frequency and severity of chemotherapy side effects.

2. The method of claim 1 wherein the sequence consists of a sequence of at least six contiguous amino acids of groups R1-R8 in the sequence of general formula I.

3. The method of claim 1 wherein the sequence consists of a sequence of at least seven contiguous amino acids of groups R1-R8 in the sequence of general formula I.

4. The method of claim 1 wherein the active agent consists of the amino acid sequence of SEQ ID NO:4.

5. The method of claim 1 wherein the active agent is administered at a dosage of between 2.5 µg/kg/day and 100 µg/kg/day.

6. The method of claim 1 wherein the active agent is administered at a dosage of between 10 µg/kg/day and 75 µg/kg/day.

7. The method of claim 1 wherein the active agent is administered parenterally.

8. The method of claim 7 wherein the active agent is administered subcutaneously or intravenously.

9. The method of claim 8 wherein the active agent is self-administered.

10. The method of claim 9 wherein the active agent is administered into the abdomen or thigh.

11. The method of claim 1 wherein administration of the active agent is initiated either at the time chemotherapy is initiated, or subsequently to initiation of chemotherapy.

12. The method of claim 1 wherein the active agent is administered once per day.

13. A pharmaceutical composition comprising a) an active agent comprising a sequence consisting of at least five contiguous amino acids of groups R1-R8 in the sequence of general formula I
R1-R2-R3-R4-R5-R6-R7-R8 Wherein
R1 is Asp; R2 is Arg; R3 is Val; R4 is Tyr; R5

is Ile; R6 is His; R7 is Pro; and R8 is Phe or is absent, excluding sequences including R4 as an N-terminal Tyr group; and wherein the active agent is not SEQ ID NO:1, in an amount sufficient to provide a dosage to a patient of between 2.5 µg/kg/day and 100 µg/kg/day, and effective to treat chemotherapy side effects, or to reduce the frequency, severity, or the frequency and severity of chemotherapy side effects; and b) a pharmaceutically acceptable carrier.

14. The pharmaceutical composition of claim 13 wherein the active agent has the amino acid sequence of SEQ ID NO:4.

15. The pharmaceutical composition of claim 13 further comprising an amount effective of a cytokine for increasing hematopoietic cell production.

16. The pharmaceutical composition of claim 15 wherein the cytokine is selected from the group consisting of granulocyte colony stimulating factor, granulocyte-**macrophage**-colony stimulating factor (GM-CSF), epidermal growth factor, interleukin 11, thrombopoietin, megakaryocyte development and growth factor, pixykines, stem cell factor, FLT (fms-like tyrosine kinase)-ligand, and interleukins 1, 3, 6, and 7.

17. The pharmaceutical composition of claim 16 wherein the cytokine is granulocyte colony stimulating factor.

18. An article of manufacture, comprising the pharmaceutical composition of claim 13 **loaded** in a drug delivery device.

19. The article of manufacture of claim 18 wherein the delivery device is a syringe.

20. The method of claim 1 wherein the side effect is hematopoietic toxicity.

21. The method of claim 1 wherein the side effect is decreased mobilization of hematopoietic progenitor cells from bone marrow into the peripheral blood.

22. The method of claim 1 wherein the side effect is anemia.

23. The method of claim 1 wherein the side effect is myelosuppression.

24. The method of claim 1 wherein the side effect is pancytopenia.

25. The method of claim 1 wherein the side effect is thrombocytopenia.

26. The method of claim 1 wherein the side effect is neutropenia.

27. The method of claim 1 wherein the side effect is lymphopenia.

28. The method of claim 1 wherein the side effect is leukopenia.

29. The method of claim 1 wherein the side effect is stomatitis.

30. The method of claim 1 wherein the side effect is alopecia.

31. The method of claim 1 wherein the side effect is headache.

32. The method of claim 1 wherein the side effect is muscle pain.

L26 ANSWER 35 OF 54 USPATFULL on STN

2004:120074 T-cell epitope of the papillomavirus l1 and e7 protein and use thereof in diagnostics and therapy.
Nieland, John, Stockdorf, GERMANY, FEDERAL REPUBLIC OF
Kaufmann, Andreas, Jena, GERMANY, FEDERAL REPUBLIC OF
Kather, Angela, Jena, GERMANY, FEDERAL REPUBLIC OF
Schinz, Manuela, Ranis, GERMANY, FEDERAL REPUBLIC OF
US 2004091479 A1 20040513
APPLICATION: US 2003-432465 A1 20031210 (10)
WO 2001-EP14037 20011130
PRIORITY: DE 2000-10059631 20001201
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A T cell epitope having an amino acid sequence

YLPPVPVSKVVSTDEYVART, STDEYVARTNIYYHAGTSRL,

VGHPYFPIKKPNNNKILVPK, GLQYRVFRIHLPDPNKFGFP,

WACVGVEVGRGQPLGVGISG, QPLGVGISGHPLLNKLDDTE,

QLCLIGCKPPIGEHWGKGSP, LELINTVIQDGDMVDTGFGA,

DMVDTGFGAMDFTTLQANKS, VTVVDTTRSTNMSLCAAIST,

TTYKNTNFKEYLRHGEEYDL, IFQLCKITLTADVMTYIHSM,

PPPGGTLEDTYRFVTSQAIA, RFVTSQAIACQKHTPPAPKE,

LKKYTFWEVNLKEKFSADLD, PLGRKFLLQAGMHGDTPTLH,

YCYEQLNDSSEEEDEIDGPA, VGNPYFRVPAGGGNKQDIPK,

GGNKQDIPKVSAYQYRVFRV, SIYNPETQRLVWACAGVETG,

IYNPETQRL, PDYLQMSADPYGDSMFFCLR,

GDSMFFCLRREQLFARHFWN, NNGVCWHNQLFVTVVDTTRS,

PPPPTTSLVDTYRFVQSVAI, YRFVQSVAITCQKDAAPAEN,

PYDKLKFWNVDLKEKFSLDL, YPLGRKFLVQAGMHGPKATL,

MHGPKATLQDIVLHLEPQNE, VDLLCHEQLSDSEEENDEID,

SEEENDEIDGVNHQHLPARR, SSADDLRAFQQLFLNTLSFV,

NTDDYVTRTSIFYHAGSSRL, FYHAGSSRLLTVGNPYFRVP,

PQRHTMLCMCCKCEARIKLV, GMHGPKATL, HGPKATLQDI,

MHGPKATL, or FQQLFLNTL and/or a functionally active variant thereof.

2. The T cell epitope as claimed in claim 1, characterized in that said variant possesses a sequence homology with

YLPPVPVSKVVSTDEYVART, STDEYVARTNIYYHAGTSRL,

VGHPYFPIKKPNNNKILVPK, GLQYRVFRIHLPDPNKFGFP,

NACVGVEVGRGQPLGVGISG, QPLGVGISGHPLLNKLDDTE,

QLCLIGCKPPIGEHWGKGSP, LELINTVIQDGDMVDTGFGA,

DMVDTGFGAMDFTTLQANKS, VTVVDTTRSTNMSLCAAIST,

TTYKNTNFKEYLRHGEEYDL, IFQLCKITLTADVMTYIHSM,

PPPGGTLEDTYRFVTSQAIA, RFVTSQAIACQKHTPPAPKE,

LKKYTFWEVNLKEKFSADLD, PLGRKFLLQAGMHGDTPTLH,

YCYEQLNDSSEEEDEIDGPA, VGNPYFRVPAGGGNKQDIPK,

GGNKQDIPKVSAYQYRVFRV, SIYNPETQRLVWACAGVEIG,

IYNPETQRL, PDYLQMSADPYGDSMFFCLR,

GDSMFFCLRREQLFARHFWN, NNGVCWHNQLFVTVVDTTRS,

PPPPTTSLVDTYRFVQSVAI, YRFVQSVAITCQKDAAPAEN,

PYDKLKFWNVDLKEKFSLDL, YPLGRKFLVQAGMHGPKATL,

MHGPKATLQDIVLHLEPQNE, VDLLCHEQLSDSEEENDEID,

SEEENDEIDGVNHQHLPARR, SSADDLRAFQQLFLNTLSFV,

NTDDYVTRTSIFYHAGSSRL, FYHAGSSRLLTVGNPYFRVP,

PQRHTMLCMCCKCEARIKLV, GMHGPKATL, HGPKATLQDI,

MHGPKATL, or FQQLFLHTL of at least approx. 65%, preferably at least approx. 75% and in particular at least approx. 85% at the amino acid level.

3. The T cell epitope as claimed in claim 1, characterized in that said variant has structural homology with

YLPPVPVSKVVSTDEYVART, STDEYVARTNIYYHAGTSRL,

VGHPYFPIKKPNNNKILVPK, GLQYRVFRIHLPDPNKFGFP,

WACVGVEVGRGQPLGVGISG, QPLGVGISGHPLLNKLDDTE,

QLCLIGCKPPIGEHWGKGSP, LELINTVIQDGDMVDTGFGA,

DMVDTGFGAMDFTTLQANKS, VTVVDTTRSTNMSLCAAIST,

TTYKNTNFKBYLRHGEEYDL, IFQLCKITLTADVMTYIHSM,

PPPGGTLEDTYRFVTSQAIA, RFVTSQAIACQKHTPPAPKE,

LKKYTFWEVNLKEKFSADLD, PLGRKFLLQAGMHGDTPTLH,

YCYEQLNDSSEEEDEIDGPA, VGNPYFRVPAGGGNKQDIPK,

GGNKQDIPKVSAYQYRVFRV, SIYNPETQRLVWACAGVEIG,

IYNPETQRL, PDYLQMSADPYGDSMFFCLR,

GDSMFFCLRREQLFARHFWN, NNGVCWHNQLFVTVVDTTRS,

PPPPTTSLVDTYRFVQSVAI, YRFVQSVAITCQKDAAPAEN,

PYDKLKFWNVDLKEKFSLDL, YPLGRKFLVQAGMHGPKATL,

MHGPKATLQDIVLHLEPQNE, VDLLCHEQLSDSEEENDEID,

SEEENDEIDGVNHQHLPARR, SSADDLRAFQQLFLNTLSFV,

NTDDYVTRTSIFYHAGSSRL, FYHAGSSRLLTVGNPYFRVP,

PQRHTMLCMCCKCEARIKLV, GMHGPKATL, HGPKATLQDI,

MHGPKATL, or FQQLFLHTL

4. The T cell epitope as claimed in one of claims 1-3, characterized in that the T cell epitope induces a cytotoxic response or mediates a T helper cell function.

5. A compound containing a T cell epitope as claimed in one of claims 1 to 4, with the compound not being any naturally occurring L1 protein derived from a papillomavirus and, in the case of an HPV-16 T cell epitope, not being any exclusively N-terminal or exclusively C-terminal deletion mutant of a naturally occurring L1 protein derived from a papillomavirus.

6. The compound as claimed in claim 5, characterized in that the compound is a polypeptide, in particular a fusion protein.

7. The compound as claimed in claim 5 or 6, characterized in that the compound is a polypeptide of at least approx. 50 amino acids, preferably of at least approx. 35 amino acids, in particular of at least approx. 20 amino acids, and, in a particularly preferred manner, of at least approx. 9-13 amino acids, in length.

8. The compound as claimed in one of claims 5-7, characterized in that the compound contains a chemical, radioactive, nonradioactive isotopic and/or fluorescent labeling of the T cell epitope and/or of said fusion protein, and/or a chemical modification of the T cell epitope and/or fusion protein.

9. A nucleic acid, characterized in that it encodes a T cell epitope as claimed in one of claims 1-4 or a compound containing a T cell epitope as claimed in one of claims 5-8.

10. A vector, in particular an expression vector, characterized in that it contains a nucleic acid as claimed in claim 9.

11. A cell, characterized in that it contains, preferably presents, at least one T cell epitope as claimed in one of claims 1-4 or a compound as claimed in one of claims 5-8.

12. The cell as claimed in claim 11, characterized in that the cell is transfected, transformed and/or infected with a nucleic acid as claimed in claim 9 and/or a vector as claimed in claim 10.

13. The cell as claimed in claim 11, characterized in that the cell was incubated with at least one T cell epitope as claimed in one of claims 1-4, at least one compound as claimed in one of claims 5-8 and/or at least one complex as claimed in one of claims 15-17 containing a T cell epitope as claimed in one of claims 5-8.

14. The cell as claimed in claim 11 or 12, characterized in that the cell is a B cell, a **macrophage**, a dendritic cell or a fibroblast, in

particular a JY cell, T2 cell, CaSki cell or EBV-transformed cell.

15. A complex comprising a T cell epitope as claimed in one of claims 1-4 or a compound as claimed in one of claims 5-8 and at least one further compound.

16. The complex as claimed in claim 15, characterized in that the complex contains at least one MHC class I molecule, preferably as HLA A2.01, A1 or A24 tetramer.

17. The complex as claimed in claim 16, characterized in that said MHC class I molecule is a human MHC class I molecule, in particular an HLA A2.01, A1 or A24 molecule.

18. A method for the in-vitro detection of the activation of T cells by at least one T cell epitope as claimed in one of claims 1-4 or by at least one compound containing a T cell epitope as claimed in one of claims 1-4, which contains the following steps: a) stimulating cells with at least one said compound; b) adding at least one target cell, which is presenting a T cell epitope as claimed in one of claims 1-4, or a complex as claimed in one of claims 15-17, and c) determining the activation of T cells.

19. The method as claimed in claim 18, characterized in that, after step a), it contains the following additional step a'): a') coculturing cells for at least approx. 1 week, in particular at least approx. 8 weeks, with: (i) at least one target cell which is **loaded** with a T cell epitope as claimed in one of claims 1-4, with a compound as claimed in one of claims 5-8, at least one complex as claimed in one of claims 15-17, at least one capsomere, at least one stable capsomere, at least one VLP, at least one CVLP and/or at least one virus, (ii) at least one complex as claimed in one of claims 15-17, (iii) and/or at least one target cell which is presenting a T cell epitope as claimed in one of claims 1-4, before step b) follows.

20. The method for preparing a target cell as claimed in one of claims 11, 13, 14, 18 or 19, characterized in that the target cell is incubated with at least one T cell epitope as claimed in one of claims 1-4, with at least one compound as claimed in one of claims 5-8 and/or at least one complex as claimed in one of claims 15-17 containing a T cell epitope as claimed in one of claims 5-8.

21. The method for preparing a target cell as claimed in one of claims 11, 12, 14, 18 or 19, characterized in that the target cells is transfected, transformed and/or infected with a nucleic acid as claimed in claim 9 and/or a vector as claimed in claim 10.

22. The method for preparing a target cell as claimed in claim 20 or 21, characterized in that the target cell is a B cell, a **macrophage**, a dendritic cell or a fibroblast, in particular a JY cell, T2 cell, CaSki cell or EBV-transformed cell.

23. The method as claimed in claim 18 or 19, characterized in that the following step a") is carried out in place of step a): a") isolating and preparing samples containing T cells and then culturing them.

24. A test system for the in-vitro detection of the activation of T cells comprising: a) at least one T cell epitope as claimed in one of claims 1-4, at least one compound as claimed in one of claims 5-8, at least one vector as claimed in claim 10, at least one cell as claimed in one of claims 11-14 and/or at least one complex as claimed in one of claims 15-17, and b) immune system effector cells, preferably T cells,

in particular cytotoxic T cells or T helper cells.

25. The use of at least one T cell epitope as claimed in one of claims 1-4, of at least one compound as claimed in one of claims 5-8, of at least one vector as claimed in claim 10, of at least one cell as claimed in one of claims 11-14, and/or of at least one complex as claimed in one of claims 15-17, for inducing or for detecting an immune response.

26. A pharmaceutical or diagnostic agent comprising at least one T cell epitope as claimed in one of claims 1-4, at least one compound as claimed in one of claims 5-8, at least one vector as claimed in claim 10, at least one cell as claimed in one of claims 11-14, and/or at least one complex as claimed in one of claims 15-17 and, where appropriate, a pharmaceutically acceptable carrier.

27. A pharmaceutical or diagnostic agent as claimed in claim 26, characterized in that at least one T cell epitope as claimed in one of claims 1-4, at least one compound as claimed in one of claims 5-8, at least one vector as claimed in claim 10, at least one cell as claimed in any one of claims 11-14, and/or at least one complex as claimed in one of claims 15-17 is present in solution, is bound to a solid matrix and/or is treated with an adjuvant.

L26 ANSWER 36 OF 54 USPATFULL on STN
2004:100785 Haptenizing cancer cell components.
Caplan, Michael J., Woodbridge, CT, UNITED STATES
Bottomly, H. Kim, New Haven, CT, UNITED STATES
US 2004076646 A1 20040422
APPLICATION: US 2002-197376 A1 20020717 (10)
PRIORITY: US 2001-306228P 20010718 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A composition comprising: a tumor cell component; and a hapten linked to the tumor cell component to form a haptenized tumor cell component, which hapten is characterized in that it maintains the ability to stimulate, support, or enhance an immune reaction in a host when linked to the tumor cell component.

2. The composition of claim 1 wherein the hapten comprises an entity selected from the group consisting of compounds that are naturally produced by poison ivy, poison oak, or poison sumac plants.

3. The composition of claim 1 wherein the hapten is a urushiol.

4. The composition of claim 1 wherein the tumor cell component comprises at least one intact cancer cell.

5. The composition of claim 1 wherein the tumor cell component comprises at least one tumor associated peptide.

6. The composition of claim 5 wherein the hapten is linked to the tumor-associated peptide as a hapten-peptide conjugate, which conjugate is present in an MHC cleft on a surface of the antigen presenting cell.

7. The composition of claim 1 further comprising an antigen presenting cell.

8. The composition of claim 7 wherein the antigen presenting cell is selected from the group consisting of dendritic cells, **macrophages**.

9. The composition of claim 7 wherein the antigen presenting cell is a dendritic cell.

10. A method of treating cancer comprising: administering to a subject suffering from cancer a composition comprising an effective amount of a tumor cell component linked to a hapten to form a haptenized tumor cell component, which hapten is characterized in that it maintains the ability to stimulate, support, or enhance an immune reaction in a host when linked to the tumor cell component.

11. The method of claim 10 wherein the hapten comprises an entity selected from the group consisting of compounds that are naturally produced by poison ivy, poison oak, or poison sumac plants.

12. The method of claim 10 wherein the hapten is a urushiol.

13. The method of claim 10 wherein the tumor cell component comprises at least one intact tumor cell.

14. The method of claim 10 wherein the tumor cell component comprises at least one tumor associated peptide.

15. The method of claim 14 wherein the hapten is linked to the tumor-associated peptide as a hapten-peptide conjugate, which conjugate is present in an MHC cleft on a surface of the antigen presenting cell.

16. The method of claim 10 further comprising administering an antigen presenting cell in combination with the haptenized tumor cell component.

17. The method of claim 16 wherein the antigen presenting cell is selected from the group consisting of dendritic cells, **macrophages**.

18. The method of claim 16 wherein the antigen-presenting cell is a dendritic cell.

19. The method of claim 16 wherein the antigen presenting cell is **loaded** in vitro with a haptenized tumor cell component.

20. The method of claim 19 wherein the antigen presenting cell is administered in vivo.

21. The method of claim 10 further comprising administering the haptenized tumor cell component with an adjuvant.

22. The method of claim 10 wherein the haptenized tumor cell component is encapsulated.

23. The method of claim 10 wherein the haptenized tumor cell component is targeted to an antigen-presenting cell.

24. The method of claim 10 wherein the haptenized tumor cell component is administered with a chemotherapeutic agent.

25. The method of claim 10 wherein the haptenized tumor cell component is administered with an anti-angiogenesis factor.

26. A composition comprising an antigen presenting cell, wherein the antigen presenting cell presents a sensitizing agent selected from the group consisting of compounds that are naturally produced by poison ivy, poison oak, or poison sumac plants.

27. The composition of claim 26 wherein the antigen presenting cell is a

dendritic cell.

28. The composition of claim 26 wherein the antigen presenting cell is a **macrophage**.

29. The composition of claim 26 wherein the sensitizing agent is a urushiol.

30. The composition of claim 26 wherein the sensitizing agent is an extract of poison ivy.

31. The method of claim 26 wherein the antigen presenting cell presents a haptenized tumor cell component.

32. The method of claim 31 wherein the haptenized tumor cell component is a haptentized tumor cell.

33. The method of claim 31 wherein the haptenized tumor cell component is a tumor associated peptide

34. The method of claim 31 wherein the antigen presenting cell is administered to a patient in vivo.

35. A method of stimulating an immune response in an individual, the method comprising: administering to a subject suffering from cancer a composition comprising and effective amount of a antigen presenting cell, wherein the antigen presenting cell presents a sensitizing agent selected from the group consisting of compounds that are naturally produced by poison ivy, poison oak, or poison sumac plants.

36. The method of claim 35 wherein the hapten is a urushiol.

37. The method of claim 35 wherein the sensitizing agent is an extract of poison ivy.

38. The composition of claim 35 wherein the antigen presenting cell is a **macrophage**.

39. The composition of claim 35 wherein the antigen presenting cell is a dendritic cell.

40. The method of claim 35 wherein the sensitizing agent is present in an MHC cleft on a surface of the antigen presenting cell.

41. The method of claim 35 wherein the antigen presenting cell is administered with an adjuvant.

42. The method of claim 35 wherein the antigen presenting cell is encapsulated.

43. The method of claim 35 wherein the sensitizing agent is targeted to an antigen-presenting cell.

44. The method of claim 35 wherein the antigen presenting cell is administered with a chemotherapeutic agent.

45. The method of claim 35 wherein the antigen presenting cell is administered with an anti-angiogenesis factor.

L26 ANSWER 37 OF 54 USPATFULL on STN
2004:94219 Cell therapy method for the treatment of tumors.

Leturcq, Didier J., San Diego, CA, UNITED STATES
Moriarty, Ann M., Poway, CA, UNITED STATES
Jackson, Michael R., Del Mar, CA, UNITED STATES
Peterson, Per A., Basking Ridge, NJ, UNITED STATES
Richard, Jon M., Glenview, IL, UNITED STATES
US 2004071671 A1 20040415
APPLICATION: US 2002-289566 A1 20021107 (10)
PRIORITY: US 2001-270252P 20010220 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A method for treating a viral infection in a subject comprising: a. preparing a non-naturally occurring antigen-presenting cell line(nnAPC), wherein said nnAPC is capable of presenting up to about fifteen different peptide molecules associated with said viral infection simultaneously wherein said peptide molecules are each about six to twelve amino acids in length, b. harvesting CD8+ cells from said subject or a suitable donor; c. stimulating said CD8+ cells with said nnAPC cell line; d. adding said CD8+ cells to media that contains a cytokine selected from the group consisting of IL-2, IL-7 or conditioned growth medium (CGM), wherein said cytokines can be used individually or in combination; e. mixing unsuspended peripheral blood **monocytes**, or CD-8 depleted peripheral blood **monocytes** collected from said subject or a suitable donor with about 1 to 50 μg/ml of one of said peptides that said nnAPC can simultaneously present; f. irradiating said peripheral blood **monocyte** suspension with a sufficient dose of γ-radiation necessary to sterilize all components in the suspension, except the desired peripheral blood **monocytes**; g. isolating adherent peripheral blood **monocytes**; h. loading said adherent peripheral blood **monocytes** with about 1 ug/ml to 50 μg/ml of said each peptide; i. combining said CD8+ cells with said adherent peripheral blood **monocytes** at a ratio of about ten CD8+ cells to one peripheral blood **monocyte**; and j. inoculating said subject with the CD8+ suspension.

2. The method of claim 1 wherein said nnAPC is capable of presenting up to about ten peptide molecules.

3. The method of claim 1 wherein said peptide molecules are about eight to ten amino acids in length

4. The method of claim 1 wherein said peptide molecules are in a concentration range of about 10 nM to 100 μM.

5. The method of claim 1 wherein said cytokine component is IL-2.

6. The method of claim 1 wherein said cytokine component is IL-2 and IL-7 in combination

7. The method of claim 1 wherein the dose of γ-radiation is about 3,000 to 7,000 rads.

8. The method of claim 1 wherein the dose of γ-radiation is about 5,000 rads.

9. A method for treating a subject with melanoma, comprising the steps of: a. administering to said subject an effective amount of interferon-alfa that is capable of enhancing the expression of tumor antigen on the surface of the tumor; and b. inoculating said subject with an effective amount of autologous cytotoxic T lymphocytes with specificity for melanoma-associated target antigen.

10. The method of claim 9, further comprising the step of administering to said subject an effective amount of interleukin-2 that is capable of enhancing the in vivo maintenance of the autologous cytotoxic T lymphocytes with specificity for melanoma-associated target antigen.

11. The method of claim 10, wherein the interferon-alfa is selected from interferon-alfa-2a or interferon-alfa-2b.

12. The method of claim 10, wherein the effective amount of interferon-alfa is about 10 MU/m2/day and is subcutaneously administered to the subject consecutively from day 5 to day 1 prior to inoculating said subject with the effective amount of autologous cytotoxic T lymphocytes with specificity for melanoma-associated target antigen.

13. The method of claim 10, wherein the effective amount of autologous cytotoxic T lymphocytes with specificity for melanoma-associated target antigen is about 1-10x109 cells/infusion.

14. The method of claim 10, wherein the autologous cytotoxic T lymphocytes with specificity for melanoma-associated target antigen are obtained by a method comprising steps of: a) preparing a non-naturally occurring antigen-presenting cell line (nnAPC), wherein said nnAPC is capable of presenting up to about fifteen different epitopes associated with said melanoma simultaneously and where each epitope is a peptide of eight to ten amino acids in length; b) loading the nnAPC with up to about fifteen different epitopes associated with said melanoma; c) harvesting CD8+ cells from said subject; d) stimulating said CD8+ cells with the epitope-**loaded** nnAPC cell line to obtain CD8+ cells specific for the melanoma; e) growing the CD8+ cells specific for the melanoma in media containing IL-2 and IL-7; f) mixing CD8-depleted peripheral blood **monocytes** collected from said subject with each epitope used for nnAPC loading; g) irradiating said CD8-depleted peripheral blood **monocytes** with γ-radiation; h) isolating adherent CD8-depleted peripheral blood **monocytes**; i) loading said adherent peripheral blood **monocytes** with each epitope used for nnAPC loading; j) restimulating said CD8+ cells specific for the melanoma with the epitope-**loaded** adherent peripheral blood **monocytes**; k) growing the restimulated CD8+ cells specific for the melanoma in media containing IL-2 and IL-7; and l) expanding the restimulated CD8+ cells specific for the melanoma by OKT3 antibody stimulation.

15. The method of claim 14, wherein step 0) can be repeated at least one more time.

16. The method of claim 14, wherein said non-naturally occurring antigen-presenting cell line is **loaded** with epitopes that are peptides derived from tyrosinase, gp100, and MART-1.

17. The method of claim 16, wherein said non-naturally occurring antigen-presenting cell line is **loaded** with epitopes comprising amino acid sequences of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 5, and SEQ ID NO: 6.

18. The method of claim 14, wherein the effective amount of interleukin-2 is about 3 MIU/day and is subcutaneously administered to the subject consecutively from day 0 to day 28 after inoculating said subject with the effective amount of autologous cytotoxic T lymphocytes with specificity for melanoma-associated target antigen.

19. The method of claim 14, wherein the method is repeated at an

interval of about 2 months.

20. The method of claim 19, wherein the method is repeated for at least two cycles and further comprises the step of evaluating a response in said subject after each cycle.

21. The method of claim 14, comprising the steps of: a. subcutaneously administering to the subject 10 MU/m2/day of interferon-alpha-2b consecutively from day 5 to day 1 prior to inoculating said subject with autologous cytotoxic T lymphocytes with specificity for melanoma-associated target antigen; b. introducing about 1-10x109 cells/infusion of the autologous cytotoxic T lymphocytes with specificity for melanoma-associated target antigen to the subject; and c. subcutaneously administering to the subject about 3 MIU/day of interleukin-2 consecutively from day 0 to day 28 following the introducing step.

L26 ANSWER 38 OF 54 USPATFULL on STN
2004:38156 Sensitization process for antigen-presenting cells and means for implementing the process.
Zitvogel, Laurence, Paris, FRANCE
Raposo, Graca, Paris, FRANCE
Regnault, Armelle, Paris, FRANCE
Amigorena, Sebastian, Paris, FRANCE
US 2004028692 A1 20040212
APPLICATION: US 2003-610709 A1 20030702 (10)
PRIORITY: FR 1997-9007 19970716
FR 1998-1437 19980206
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. Vesicle derived from a tumor cells characterized in that: it is freed from its natural environment, and it consists of a lipid bilayer which surrounds a cytosolic fraction.

2. Vesicle according to claim 1, characterized in that it presents on its surface class I and/or class II molecules of the major histocompatibility complex (MHC).

3. Vesicle according to claim 1 or 2, characterized in that it presents on its surface in addition adhesion molecules and/or lymphocytic costimulatory molecules.

4. Vesicles according to one of the claims 1 to 3, characterized in that it presents on its surface in addition antigenic peptides, optionally associated with class I/II molecules of the MHC.

5. Vesicle according to one of the claims 1 to 4, characterized in that it contains in its cytosolic fraction tumor antigenic molecules and/or immunomodulators and/or chemo-attractants and/or hormones and/or nucleic acids.

6. Vesicle derived from a tumor cell, characterized in that it possesses a diameter included between 60 and 90 nm, it presents on its surface antigenic peptides characteristic of tumors in combination with class I and/or class II molecules of the major histocompatibility complex (MHC) and it presents on its surface lymphocytic costimulatory molecules.

7. Vesicle according to claim 6, characterized in that it contains the protein HSP70.

8. Vesicle according to claim 6 or 7, characterized in that it lacks protein gp96.

9. Vesicle according to any one of the preceding claims, characterized in that it contains in addition a heterologous nucleic acid.

10. Preparation process for vesicles according to one of the claims 1 to 9 (texosomes) comprising a first step in which a biological sample is provided and a second step involving the isolation of texosomes from said sample.

11. Process according to claim 10, characterized in that the biological sample consists of membrane fractions, culture supernatants or tumor cell lysates or even fresh tumor suspensions.

12. Process according to claim 10 or 11, characterized in that the biological sample is treated with one or more agents which stimulate the production of texosomes.

13. Process according to claim 10, characterized in that the isolation is carried out by centrifugation, electrophoresis, chromatography and/or nanofiltration.

14. Antigen-presenting cell **loaded** with vesicles (texosomes) according to one of the claims 1 to 9.

15. Preparation process for an antigen-presenting cell according to claim 14, comprising the steps of incubation of antigen-presenting cells in the presence of one or more texosomes according to one of the claims 1 to 7 and recovery of above-mentioned **loaded** antigen-presenting cells thus obtained.

16. Membrane vesicle freed from its natural environment, secreted by antigen-presenting cells **loaded** with vesicles according to one of the claims 1 to 9.

17. Membrane vesicle (designated dexosome), characterized in that it is derived from a dendritic cell, it comprises one or more class I molecules of the major histocompatibility complex, and it comprises one or more class II molecules of the major histocompatibility complex.

18. Vesicle according to claim 17, characterized in that it comprises in addition one or more CD63 molecules.

19. Vesicle according to claim 17 or 18, characterized in that it comprises, in addition, one or more CD82 and/or CD86 molecules, and preferably at least CD86.

20. Vesicle according to one of the claims 17 to 19, characterized by a diameter included between 60 and 90 nm.

21. Vesicle according to one of the claims 17 to 20, characterized in that it comprises in addition one or more antigenic peptides.

22. Vesicle according to one of the claims 17 to 21, characterized in that it is derived from an immature dendritic cell.

23. Vesicle according to one of the claims 17 to 22, characterized in that it is derived from a dendritic cell bearing one or more antigenic peptides.

24. Vesicle according to claim 23, characterized in that it is derived

from a dendritic cell incubated with a vesicle according to claim 1.

25. Vesicle according to claim 23, characterized in that it is derived from an immortalized dendritic cell.

26. Preparation process for a vesicle according to one of the claims 17 to 25, comprising a first step of isolation of dendritic cells or of a cell culture comprising dendritic cells, and optional second step during which the cells may be sensitized to antigens of interest, and a third step comprising the production of vesicles from these cell cultures.

27. Process according to claim 26, characterized in that the first step comprises the isolation of dendritic cells from **monocyte** precursors or bone marrow.

28. Process according to claim 26 or 27, characterized in that the first step comprises the isolation of immature dendritic cells, preferably human.

29. Process according to claim 26 to 28, characterized in that the sensitization step is achieved by placing the dendritic cells in contact with peptides, antigens, cells or membranes or vesicles expressing antigens or antigenic peptides, liposomes or nucleic acids, optionally incorporated into chemical or viral vectors.

30. Process according to one of the claims 26 to 29, characterized in that the vesicle preparation step comprises a first, facultative step involving treatment of the cells, followed by a second step involving isolation of the vesicles.

31. Process according to claim 30, characterized in that the dendritic cells are treated by being cultured in the presence of cytokines favouring the immature state, by irradiation or by reducing the pH of the culture, or by combining these different types of treatment.

32. Process according to claim 30, characterized in that the isolation of the vesicles is achieved according to claim 13.

33. Preparation process for membrane vesicles derived from a cell comprising at least one separation step by means of electrophoresis, chromatograppphy or nanofiltration.

34. Use of: texosomes according to one of the claims 1 to 9, or antigen-presenting cells according to claim 14, or dexosomes according to one of the claims 16 to 25, for the stimulation and optionally amplification in vitro of T lymphocytes specific for antigens contained in the above-mentioned texosomes, antigen-presenting cells or dexosomes or B lymphocytes, and in particular for the stimulation and amplification of T lymphocytes in vitro.

35. Use of texosomes according to one of the claims 1 to 9, or of antigen-presenting cells according to claim 14, or of dexosomes according to one of the claims 16 to 25 for the ex vivo selection of a T lymphocyte directory, capable of recognizing specific antigens contained in the above-mentioned texosomes, antigen-presenting cells or dexosomes.

36. Medicine containing as active substance one or more texosomes according to one of the claims 1 to 9, antigen-presenting cells according to claim 14, and/or dexosomes according to one of the claims 16 to 25, in combination with a pharmaceutically acceptable vehicle.

37. Medicine according to claim 36 for the treatment of cancers and

parasitic and infectious diseases.

38. Medicine according to claim 35 or 36, characterized in that it contains a stabilizing agent in addition.

39. Combination of texosomes and/or dexosomes and an immunostimulating adjuvant for the purpose of simultaneous use, separate use or use of each at intervals.

40. Use of a dexosome according to one of the claims 16 to 25 for the preparation of a pharmaceutical composition designed for the treatment of cancers and parasitic and infectious diseases.

41. Use of gamma interferon, interleukin 10 and/or interleukin 12 for the production of dexosomes.

L26 ANSWER 39 OF 54 USPATFULL on STN
2004:30676 Shed antigen vaccine with dendritic cells adjuvant.
Bystryn, Jean-Claude, New York, NY, UNITED STATES
US 2004022813 A1 20040205
APPLICATION: US 2002-213388 A1 20020805 (10)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A method for producing a composition for use as a vaccine for treatment or prevention of cancer, comprising: a. collecting antigens released or shed by the type of tumor cell against which it is desired to prepare the vaccine; b. preparing mammalian dendritic cells in a culture from a mammalian blood, bone marrow or other tissue sample by culturing the blood, bone marrow, or other tissue sample under conditions that cause differentiation and proliferation of dendritic cells; c. separating dendritic cells from other cells in the culture; and d. exposing the dendritic cells to the shed antigens collected as described in paragraph a. above under conditions that result in the combination of the shed cancer antigens or their fragments and the dendritic cells.

2. A method in accordance with claim 1, wherein the blood, bone marrow or other tissue sample is taken from the patient receiving the treatment or from an unrelated donor.

3. A method in accordance with claim 1, wherein the shed cancer antigens are obtained from one or more melanoma cell lines.

4. A method in accordance with claim 1 wherein the shed mammalian cancer antigens are obtained from one or more breast cancer cell lines.

5. A method in accordance with claim 1 wherein the shed mammalian cancer antigens are obtained from one or more lung cancer cell lines.

6. A method in accordance with claim 1 wherein the shed mammalian cancer antigens are obtained from one or more prostate cancer cell lines.

7. A method in accordance with claim 1 wherein the shed mammalian cancer antigens are obtained from one or more colon cancer cell lines.

8. A method in accordance with claim 1 wherein the shed mammalian cancer antigens are obtained from one or more ovarian cancer cell lines.

9. A method in accordance with claim 1 wherein the shed mammalian cancer antigens are obtained from one or more cancer cell lines of other

histological type.

10. A method in accordance with claim 1 wherein the shed antigens are obtained from one or more pathogenic strain of bacteria, mycobacteria, fungi, virus, or other pathogenic organism.

11. A method in accordance with claim 1 wherein the shed antigens are obtained from one or more normal cell lines to treat an auto-immune disease.

12. A method in accordance with claim 1 wherein the shed cancer, infectious organism or normal tissue antigens are **loaded** onto antigen presenting cells including **macrophages**, Langerhan's cells, or other types of antigen presenting cells.

13. A method in accordance with claim 1 wherein the shed antigen vaccine **loaded** onto dendritic or other type of antigen presenting cell is co-administered with immunomodulators that can upregulate vaccine-induced immune responses such as IL-2 or GM-CSF.

14. A method in accordance with claim 12 wherein the shed antigen vaccine **loaded** onto dendritic or other type of antigen presenting cells is co-administered with immunomodulators that can upregulate vaccine-induced immune responses such as IL-2 or GM-CSF. (Same as claim 13, but dependent on claim 12)

15. A method in accordance with claim 1 wherein the shed antigens are collected from several different lines of tumor cells which shed different but complimentary patterns of tumor antigens so as to broaden the spectrum of tumor antigens in the vaccine preparation.

16. A method in accordance with claim 1 wherein the cells: a. are adapted to long-term growth in serum-free medium; and b. are treated at an acid pH, or with certain enzymes or other agents which accelerate or enhance the release of material from the cell-surface.

17. A method for treating tumor in a patient comprising administering an effective an effective amount of a vaccine made in accordance with claim 1.

18. A method in accordance for treating cancer comprising administering an effective amount of a vaccine produced in accordance with claim 1.

19. A method for producing an immune response in a patient comprising administering an effective amount of a vaccine made in accordance with the method of claim 1.

20. A method in accordance with claim 19, wherein dendritic cells present shed tumor antigens to the immune system with dendritic cells.

21. A vaccine for treating cancer in a patient, comprising a composition made in accordance with the method of claim 1 in a pharmaceutically acceptable vehicle.

L26 ANSWER 40 OF 54 USPATFULL on STN
2003:335002 Compositions and methods relating to ABCA1-mediated cholesterol efflux.
Tabas, Ira, New City, NY, UNITED STATES
Feng, Bo, Teaneck, NJ, UNITED STATES
US 2003235878 A1 20031225
APPLICATION: US 2003-426415 A1 20030430 (10)

PRIORITY: US 2002-376984P 20020430 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A method for determining whether an agent increases ABCA1-dependent cholesterol efflux from a cell comprising the steps of: (a) contacting a free cholesterol-**loaded** cell with the agent in the presence of a cholesterol acceptor which binds to cholesterol effluxed from a cell via an ABCA1-dependent pathway; (b) quantitatively determining the efflux of cholesterol from the cell; and (c) comparing the efflux so determined with a known standard, thereby determining whether the agent increases cholesterol efflux from the cell.

2. The method of claim 1, wherein the cholesterol acceptor of step (a) is selected from the group consisting of apolipoprotein A-I, apolipoprotein A-II, apolipoprotein A-IV, apolipoprotein E, a recombinant apolipoprotein and a synthetic apolipoprotein.

3. The method of claim 2, wherein the cholesterol acceptor of step (a) is apolipoprotein A-I.

4. The method of claim 1, wherein the known standard of step (c) comprises the cholesterol efflux from a free cholesterol-**loaded** cell in the absence of the agent and in the presence of a cholesterol acceptor.

5. The method of claim 1, wherein the free cholesterol-**loaded** cell is produced by (a) contacting a cell with a cholesterol-containing particle, whereby the particle enters the cell, and (b) contacting the cell with an acyl-CoA-cholesterol acyltransferase inhibitor so as to inhibit the activity of acyl-CoA-cholesterol acyltransferase in the cell, wherein steps (a) and (b) are performed concurrently or in any other order.

6. The method of claim 5, wherein the cholesterol-containing particle is an acetyl low density lipoprotein.

7. The method of claim 1, wherein (i) the free cholesterol-**loaded** cell comprises detectably labeled cholesterol and (ii) quantitatively determining the efflux of cholesterol from the cell comprises quantitatively determining the efflux from the cell of the detectably labeled cholesterol.

8. The method of claim 7, wherein the detectable label is a radioisotope.

9. The method of claim 8, wherein the radioisotope is tritium or carbon-14.

10. The method of claim 1, wherein the cell is selected from the group consisting of a **macrophage**, a hepatic cell and a smooth muscle cell.

11. The method of claim 10, wherein the cell is a **macrophage**.

12. The method of claim 1, wherein the cell is a human cell.

13. A method for increasing cholesterol efflux from a cell comprising contacting the cell with an agent which increases ABCA1-dependent cholesterol efflux from a cell.

14. A method for decreasing the amount of cholesterol in a cell comprising contacting the cell with an agent which increases

ABCA1-dependent cholesterol efflux from the cell.

15. The method of claim 13 or 14, wherein the agent is an inhibitor of an intracellular cholesterol trafficking pathway.

16. The method of claim 15, wherein the intracellular cholesterol trafficking pathway is mediated by a Niemann-Pick C molecule, lysobisphosphatidic acid, and/or lysosomal sphingomyelinase.

17. The method of claim 13 or 14, wherein the cell is selected from the group consisting of a **macrophage**, a hepatic cell and a smooth muscle cell.

18. The method of claim 17, wherein the cell is a **macrophage**.

19. The method of claim 13 or 14, wherein the cell is a human cell.

20. The method of claim 13 or 14, wherein the agent is U18666A or a pharmaceutically acceptable salt thereof.

21. The method of claim 20, wherein the agent, when contacted with the cell, is at a concentration of from about 30 nM to about 120 nM.

22. The method of claim 21, wherein the agent, when contacted with the cell, is at a concentration of about 70 nM.

23. The method of claim 13 or 14, wherein the agent is imipramine or a pharmaceutically acceptable salt thereof.

24. The method of claim 23, wherein the agent, when contacted with the cell, is at a concentration of from about 2 μM to about 20 μM.

25. The method of claim 24, wherein the agent, when contacted with the cell, is at a concentration of about 8 μM.

26. A method for increasing the likelihood that a cholesterol-**loaded** **macrophage** will survive comprising contacting the **macrophage** with an agent which increases ABCA1-dependent cholesterol efflux from a **macrophage**, thereby increasing the likelihood that the **macrophage** will survive.

27. A method for decreasing the likelihood that a cholesterol-**loaded** **macrophage** will contribute to the progression of atherosclerosis in a subject comprising contacting the **macrophage** with an agent which increases ABCA1-dependent cholesterol efflux from a **macrophage**, thereby decreasing the likelihood that the **macrophage** will contribute to the progression of atherosclerosis in the subject.

28. The method of claim 26 or 27, wherein the agent is an inhibitor of an intracellular cholesterol trafficking pathway mediated by a Niemann-Pick C molecule, lysobisphosphatidic acid, and/or lysosomal sphingomyelinase.

29. The method of claim 26 or 27, wherein the agent is U18666A or a pharmaceutically acceptable salt thereof.

30. The method of claim 29, wherein the agent, when contacted with the cell, is at a concentration of from about 30 nM to about 120 nM.

31. The method of claim 30, wherein the agent, when contacted with the cell, is at a concentration of about 70 nM.

32. The method of claim 26 or 27, wherein the agent is imipramine or a pharmaceutically acceptable salt thereof.

33. The method of claim 32, wherein the agent, when contacted with the cell, is at a concentration of from about 2 μM to about 20 μM.

34. The method of claim 33, wherein the agent, when contacted with the cell, is at a concentration of about 8 μM.

35. The method of claim 27, wherein the subject is a human.

36. The method of claim 27, wherein the agent is admixed with a pharmaceutically acceptable carrier.

37. A method for treating a subject afflicted with atherosclerosis comprising administering to the subject a therapeutically effective amount of an agent which increases ABCA1-dependent cholesterol efflux from a cell, thereby treating the subject.

38. The method of claim 37, wherein the cell is a **macrophage** cell.

39. The method of claim 37, wherein the agent is an inhibitor of an intracellular cholesterol trafficking pathway mediated by a Niemann-Pick C molecule, lysobisphosphatidic acid, and/or lysosomal sphingomyelinase.

40. The method of claim 37, wherein the agent is U18666A or a pharmaceutically acceptable salt thereof.

41. The method of claim 37, wherein the agent is imipramine or a pharmaceutically acceptable salt thereof.

42. The method of claim 37, wherein the subject is a human.

43. The method of claim 37, wherein the therapeutically effective amount of the agent is less than about 3.75 mg of agent per kg of the subject's body weight.

44. The method of claim 43, wherein the therapeutically effective amount of the agent is about 0.75 mg of agent per kg of the subject's body weight.

45. The method of claim 37, wherein the agent is admixed with a pharmaceutically acceptable carrier.

46. An article of manufacture comprising packaging material and a pharmaceutical agent, wherein the pharmaceutical agent increases ABCA1-dependent cholesterol efflux from a cell and wherein the packaging material comprises a label indicating that the pharmaceutical agent is intended for use in treating a subject afflicted with atherosclerosis.

47. The article of claim 46, wherein the cell is a **macrophage**.

48. The article of claim 46, wherein the agent is an inhibitor of an intracellular cholesterol trafficking pathway mediated by a Niemann-Pick C molecule, lysobisphosphatidic acid, and/or lysosomal sphingomyelinase.

49. The article of claim 46, wherein the agent is U18666A or a pharmaceutically acceptable salt thereof.

50. The article of claim 46, wherein the agent is imipramine or a pharmaceutically acceptable salt thereof.

51. The article of claim 46, wherein the subject is a human.

L26 ANSWER 41 OF 54 USPATFULL on STN
2003:288245 Drug releasing biodegradable fiber implant.
Nelson, Kevin D., Arlington, TX, UNITED STATES
Romero-Sanchez, Andres A.A., Arlington, TX, UNITED STATES
Smith, George M., Lexington, KY, UNITED STATES
Alikacem, Nadir, Allen, TX, UNITED STATES
Radulescu, Delia, Arlington, TX, UNITED STATES
Waggoner, Paula, Burleson, TX, UNITED STATES
Hu, Zhibing, Denton, TX, UNITED STATES
US 2003203003 A1 20031030
APPLICATION: US 2003-428354 A1 20030502 (10)
PRIORITY: US 1999-147827P 19990806 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. An implant composition comprising a scaffold comprising biodegradable polymer fibers, said fibers containing one or more therapeutic agent that are released over time.

2. The composition of claim 1, wherein said scaffold comprises woven fibers.

3. The composition of claim 1, wherein said scaffold comprises non-woven fibers.

4. The composition of claim 1, wherein said scaffold comprises knitted fibers.

5. The composition of claim 1, wherein said fibers comprise two or more subsets of said fibers, said subsets of fibers differing in biodegradable polymer content.

6. The composition of claim 1, wherein said fibers or a subset of said fibers comprise one or more co-axial or other multicomponent biodegradable polymer layers.

7. The composition of claim 1, wherein said fibers or a subset of said fibers comprise fibers containing one or more therapeutic agents, wherein the content of said one or more therapeutic agents within said fibers or said subset of fibers varies along the longitudinal axis of said fibers or subset of fibers.

8. The composition of claim 7, wherein said one or more therapeutic agents varies linearly or exponentially as a function of distance down the longitudinal axis of the fiber such that the content of said one or more therapeutic agents decreases from the first ends of said fibers or subset of said fibers to the second ends of said fibers or subset of said fibers.

9. The composition of claim 7, wherein said one or more therapeutic agents vary in a bidirectional manner, wherein the content of said one or more therapeutic agents increases from the first ends of said fibers or subset of said fibers to a maximum and then decreases towards the second ends of said fibers or subset of said fibers.

10. The composition of claim 1, wherein a subset of said fibers contains no therapeutic agent.

11. The composition of claim 1, wherein said one or more therapeutic

agents are selected from the group consisting of growth factors, immunomodulators, compounds promoting angiogenesis, compounds inhibiting angiogenesis, anti-inflammatory compounds, antibiotics, cytokines, anti-coagulation agents, procoagulation agents, chemotactic agents, agents to promote apoptosis, agents to inhibit apoptosis, and mitogenic agents.

12. The composition of claim 1, wherein said one or more therapeutic agents include a radioactive agent or a contrast agent for imaging studies.

13. The composition of claim 1, wherein said one or more therapeutic agents is selected from the group consisting of viral vector, polynucleotide and polypeptide.

14. The composition of claim 1, wherein said one or more therapeutic agents comprise an agent that promotes angiogenesis.

15. The composition of claim 14, wherein said agent that promotes angiogenesis is vascular endothelial growth factor.

16. The composition of claim 1, wherein said biodegradable polymer is a single polymer or a co-polymer or blend of polymers, wherein said polymer is selected from the group consisting of poly(L-lactic acid), poly(DL-lactic acid), polycaprolactone, poly(glycolic acid), polyanhydride, chitosan, and sulfonated chitosan.

17. A drug-delivery fiber composition comprising one or more biodegradable polymer fibers containing one or more therapeutic agents, wherein the content of said one or more therapeutic agents within said fiber varies along the longitudinal axis of said fiber such that the content of said one or more therapeutic agents decreases from the first end of said fiber to the second end of said fiber.

18. The composition of claim 17, wherein at least one subset of said fiber comprises one or more co-axial layers or other multicompent configurations of biodegradable polymers.

19. A method of controlling the spatial and temporal concentration of one or more therapeutic agents within a fiber-scaffold implant, comprising implanting a fiber-scaffold into a host, wherein said fiber-scaffold comprises biodegradable polymer fibers containing one or more therapeutic agents, wherein said one or more therapeutic agents are distributed in said fiber-scaffold in a defined nonhomogeneous pattern, which may or may not be homogeneous with regard to fiber type and distribution.

20. The method of claim 19, wherein said scaffold comprises woven fibers.

21. The method of claim 19, wherein said scaffold comprises non-woven fibers.

22. The method of claim 19, wherein said scaffold comprises knitted fibers.

23. The method of claim 19, wherein said scaffold comprises two or more subsets of said fibers, said subsets of fibers differing in biodegradable polymer content.

24. The method of claim 19, wherein said fibers or subset of said fibers comprise a plurality of at least one co-axial layer or other

multi-component configuration consisting of one or more biodegradable polymer layers.

25. The method of claim 19, wherein said fibers or a subset of said fibers comprise fibers containing one or more therapeutic agents, wherein the content of said one or more therapeutic agents within said fibers or said subset of fibers varies along the longitudinal axis of said fibers or subset of fibers.

26. The method of claim 25, wherein said one or more therapeutic agents gents varies linearly or exponentially as a function of distance down the longitudinal axis of the fiber such that the content of said one or more therapeutic agents decreases from the first ends of said fibers or subset of said fibers to the second ends of said fibers or subset of said fibers.

27. The method of claim 25, wherein said one or more therapeutic agents vary in a bidirectional manner, wherein the content of said one or more therapeutic agents increases from the first ends of said fibers or subset of said fibers to a maximum and then decreases towards the second ends of said fibers or subset of said fibers.

28. The method of claim 19, wherein a subset of said fibers contains no therapeutic agent.

29. The method of claim 19, wherein said one or more therapeutic agents are selected from the group consisting of growth factors, immunmodulators, compounds promoting angiogenesis, compounds inhibiting angiogenesis, anti-inflammatory compounds, antibiotics, cytokines, anti-coagulation agents, procoagulation agents, chemotactic agents, agents to promote apoptosis, agents to inhibit apoptosis, and mitogenic agents.

30. The method of claim 19, wherein said one or more therapeutic agents include a radioactive agent(s) or a contrast agent for imaging studies.

31. The method of claim 19, wherein said one or more therapeutic agents is selected from the group of viral vector, polynucleotide and polypeptide.

32. The method of claim 19, wherein said one or more therapeutic agents comprise an agent that promotes angiogenesis.

33. The method of claim 32, wherein said agent that promotes angiogenesis is vascular endothelial growth factor.

34. The method of claim 19, wherein said biodegradable polymer is single polymer or a co-polymer or blend of polymers selected from the group consisting of poly(L-lactic acid), poly(DL-lactic acid), polycaprolactone, poly(glycolic acid), polyanhydride, chitosan, and sulfonated chitosan.

35. A method of preparing a fiber-scaffold for preparing an implant capable of controlling the spatial and temporal concentration of one or more therapeutic agents, comprising providing biodegradable polymer fibers containing one or more therapeutic agents and forming said biodegradable polymer fibers into a three dimensional fiber-scaffold, wherein said one or more therapeutic agents are distributed in said fiber-scaffold in a defined nonhomogeneous pattern, which may or may not be homogeneous with regard to fiber type or biological material content.

36. The method of claim 35, wherein said scaffold comprises woven

fibers.

37. The method of claim 35, wherein said scaffold comprises non-woven fibers.

38. The method of claim 35, wherein said scaffold comprises knitted fibers.

39. The method of claim 35, wherein said fibers comprise two or more subsets of said fibers, said subsets of fibers differing in biodegradable polymer content.

40. The method of claim 35, wherein said fibers or a subset of said fibers comprise a plurality of co-axial or other multi-component configuration of biodegradable polymer layers.

41. The method of claim 35, wherein said fibers or a subset of said fibers comprise fibers containing one or more therapeutic agents, wherein the content of said one or more therapeutic agents within said fibers or said subset of fibers varies along the longitudinal axis of said fibers or subset of fibers.

42. The method of claim 41, wherein said one or more therapeutic agents varies linearly or exponentially as a function of distance down the longitudinal axis of the fiber such that the content of said one or more therapeutic agents decreases from the first ends of said fibers or subset of said fibers to the second ends of said fibers or subset of said fibers.

43. The method of claim 41, wherein said one or more therapeutic agents vary in a bidirectional manner, wherein the content of said one or more therapeutic agents increases from the first ends of said fibers or subset of said fibers to a maximum and then decreases towards the second ends of said fibers or subset of said fibers.

44. The method of claim 35, wherein a subset of said fibers contains no therapeutic agent.

45. The method of claim 35, wherein said one or more therapeutic agents are selected from the group consisting of growth factors, immunomodulators, compounds promoting angiogenesis, compounds inhibiting angiogenesis, anti-inflammatory compounds, antibiotics, cytokines, anti-coagulation agents, procoagulation agents, chemotactic agents, agents to promote apoptosis, agents to inhibit apoptosis, and mitogenic agents.

46. The method of claim of claim 35, wherein said one or more therapeutic agents include a radioactive agent(s) or a contrast agent for imaging studies.

47. The method of claim 35, wherein said one or more therapeutic agents is selected from the group of viral vector, polynucleotide and polypeptide.

48. The method of claim 35, wherein said one or more therapeutic agents comprise an agent that promotes angiogenesis.

49. The method of claim 48, wherein said agent that promotes angiogenesis is vascular endothelial growth factor.

50. The method of claim 35, wherein said biodegradable polymer is single polymer or a co-polymer or blend of polymers selected from the group

consisting of poly(L-lactic acid), poly(DL-lactic acid), polycaprolactone, poly(glycolic acid), polyanhydride, chitosan, and sulfonated chitosan.

51. A method of creating a drug releasing fiber from chitosan comprising use of hydrochloric acid as a solvent and Tris base as a coagulating bath.

52. The method of claim 51, wherein the hydrochloric acid concentration is from about 0.25% to about 5%.

53. The method of claim 52, wherein said hydrochloric acid concentration is further defined as from about 1% to about 2%.

54. The method of claim 51, wherein the tris base concentration is from about 2% to about 25%.

55. The method of claim 54, wherein the tris base concentration is from about 4% to about 17%.

56. The method of claim 55, wherein the tris base concentration is from about 5% to about 15%.

57. The method of claim 51, comprising using a heterogeneous mixture comprising chitosans with different degrees of deacetylation.

58. The method of claim 51, comprising creating a drug releasing fiber comprising segments of chitosan with different degrees of deacetylation.

59. The method of claim 51, comprising creating a drug releasing fiber from chitosan and an extracellular matrix.

60. he method of claim 59, wherein the chitosan concentration is from about 0.5 wt. % to about 10 wt. %.

61. The method of claim 60, wherein the chitosan concentration is from about 1 wt. % to about 7 wt. %.

62. The method of claim 61, wherein the chitosan concentration is from about 2 wt. % to about 5 wt. %.

63. The method of claim 62, wherein the chitosan concentration is from about 3 wt. % to about 4 wt. %.

64. The method of claim 63, wherein the chitosan concentration is about 3.5 wt. %.

65. The method of claim 59, wherein said extracellular matrix comprises Matrigel.

66. The method of claim 59 or 65, wherein the extracellular matrix concentration is from about 1 vol. % to about 20 vol. %.

67. The method of claim 65, wherein the extracellular matrix concentration is from about 2 vol. % to about 15 vol. %.

68. The method of claim 67, wherein the extracellular matrix concentration is from about 3 vol. % to about 10 vol. %.

69. The method of claim 68, wherein the extracellular matrix concentration is from about 4 vol. % to about 6 vol. %.

70. The method of claim 69, wherein the extracellular matrix concentration is about 5 vol. %.

71. The method of claim 59, comprising coating said fiber with said extracellular matrix.

72. The method of claim 59, wherein said chitosan is sulfated chitosan.

73. The method of claim 72, wherein the sulfated chitosan concentration is from about 0.025 wt. % to about 2 wt. %.

74. The method of claim 73, wherein the sulfated chitosan concentration is from about 0.05 wt. % to about 1 wt. %.

75. The method of claim 74, wherein the sulfated chitosan concentration is from about 0.1 wt. % to about 0.5 wt. %.

76. The method of claim 75, wherein the sulfated chitosan concentration is from about 0.15 wt. % to about 0.3 wt. %.

77. The method of claim 76, wherein the sulfated chitosan concentration is 0.2 wt. %.

78. The method of claim 71, wherein the chitosan and sulfated chitosan are extruded into a fiber.

79. A method of creating a drug releasing fiber comprising adding poly(L-lactic acid) microspheres **loaded** with drug or proteins as a drug delivery reservoir to a solution of chitosan in acid and using a sodium hydroxide coagulation bath.

80. The method of claim 79, comprising adding about 3.5 wt. % chitosan in about 2 vol. % acid and using about a 5 vol. % sodium hydroxide as a coagulation bath.

81. The method of claim 79, wherein said acid is acetic acid.

82. The method of claim 79, wherein said acid is hydrochloric acid.

83. The method of claim 82, wherein said acid in said solution comprises from about 1 vol. % to about 2 vol. % hydrochloric acid.

84. The method of claim 83, comprising adding poly(L-lactic acid)drug **loaded** microspheres to a solution of about 3.5 wt. % chitosan in from about 1 vol. % hydrochloric acid to about 2 vol. % hydrochloric acid and using a coagulation bath comprising from about 5 vol. % tris base to about 15 vol. % tris base.

85. The method of claim 79, further comprising adding a surfactant to said solution.

86. The method of claim 85, wherein said surfactant comprises albumin.

87. The method of claim 86, wherein said solution comprises about 3 wt. % of said albumin.

88. The method of claim 87, wherein said solution comprises about 1.2 vol. % hydrochloric acid.

89. A composition comprising a fiber containing chitosan and an extracellular matrix.

90. The composition of claim 89, further defined as comprising sulfated chitosan.

91. A composition comprising a three-dimensional scaffold, said scaffold comprising fibers that are woven, non-woven,. or knitted, or braided wherein said fibers comprise a composition comprising a fiber containing chitosan and an extracellular matrix.

92. The composition of claim 91, wherein said chitosan is sulfated chitosan.

93. A composition comprising fibers containing chitosan, extracellular matrix and a biological molecule.

94. The composition of claim 93, wherein said chitosan is sulfated chitosan.

95. A composition comprising a heterogeneous scaffold of fibers according to any one of claims 89, 90, 92, 93, or 94, wherein the biological molecule is not the same for all fibers of the scaffold.

96. A composition of chitosan fibers comprising microspheres of a second polymer, said microspheres comprising one or more biological molecules.

97. The composition of claim 96, further comprising a surfactant that is a biological molecule.

98. The composition of claim 97, further comprising an extracellular matrix.

99. The composition of claim 97, wherein said chitosan is sulfated chitosan.

100. The composition of claim 96, wherein the second polymer is either poly(L-lactic acid), poly(D-lactic acid), poly(glycolic acid), poly(caprolactone), or any combination of copolymers or blends of these polymers.

101. A method of fabricating fibers, comprising: a) obtaining a water-in-oil type emulsion comprising an aqueous phase containing an active biomolecule and a surfactant in a biodegradable polymer solution; and b) extruding said emulsion into a coagulating bath.

102. The method of claim 101, wherein the biodegradable polymer may be any synthetic biodegradable polymer.

103. The method of claim 101, wherein the polymer solvent for the polymer solution is a good solvent for the polymer, is substantially immiscible with water and is highly miscible with the coagulating bath solvent.

104. The method of claim 101, wherein the surfactant may be selected from the group consisting of bovine serum albumin (BSA), poly(vinyl alcohol), pluronics, or a naturally occurring surfactant.

105. The method of claim 104, wherein the surfactant is a naturally occurring surfactant.

106. The method of claim 105, wherein the naturally occurring surfactant is a phospholipid.

107. The method of claim 101, wherein the coagulating bath solvent is a

non-solvent for the polymer and highly miscible with the polymer solvent.

108. The method of claim 102, wherein the polymer is at least one polymer selected from the group consisting of poly(L-lactic acid), poly(DL-lactic acid), poly(glycolic acid), polycaprolactone, and polyanhydride.

109. The method of claim 108, wherein the polymer may be a copolymer or blend of any polymer selected from the group consisting of poly(L-lactic acid), poly(DL-lactic acid), poly(glycolic acid), polycaprolactone and polyanhydride.

110. The method of claim 103, wherein the polymer solvent is chloroform or methylene chloride.

111. The method of claim 107, wherein the coagulating bath solvent is hexane, an alcohol or acetone.

112. The method of claim 111, wherein the coagulating bath solvent is an alcohol.

113. The method of claim 112, wherein the coagulating bath solvent is isopropyl alcohol.

114. The method of claim 101, wherein the polymer solvent system comprises at least one solvent that is good for the polymer and at least one solvent that is poor for the polymer.

115. The method of claim 114, wherein the good solvent is chloroform or methylene chloride and the poor solvent is toluene.

116. The method of claim 101, wherein the coagulation bath system further comprises the polymer solvent.

117. The method of claim 116, wherein the coagulation bath comprises up to 20% v/v of the polymer solvent.

118. The method of claim 101, wherein the ocagulation coagulation bath solvent system further comprises a viscous solvent.

119. The method of claim 118, wherein the viscous solvent is glycerol.

120. The method of claim 119, wherein the glycerol concentration is between about 8% and about 20% v/v.

121. A method of fabricating fibers with a linear gradient of bioactive molecules, said method comprising: a) obtaining a first polymer solution and a second polymer solution; and b) mixing said first polymer solution and said second polymer solution in a continuously changing ratio to obtain a mixture of said first and second polymer solutions, while extruding said mixture into a coagulating bath.

122. The method of claim 121, wherein at least one of said first polymer solution and said second polymer solution is a water-in-oil type emulsion of an aqueous phase comprising an active biomolecule of interest and a surfactant in a biodegradable polymer solution.

123. The method of claim 121, wherein the second polymer comprises a surfactant and lacks an active biomolecule, or contains a different active biomolecule.

124. The method of claim 122, wherein the ratio of said first polymer solution and said second polymer solution are is controlled mixed using a butterfly valve.

125. The method of claim 122, wherein said first polymer solution and said second polymer solution are contained in separate pumps and are mixed in a mixing chamber.

126. The method of claim 121, wherein the polymer is a synthetic biodegradable polymer.

127. The method of claim 121, wherein the polymer solution comprises a good solvent for the polymer, said solvent being substantially immiscible with water and highly miscible with the coagulating bath.

128. The method of claim 121, wherein the surfactant may be selected from the group consisting of bovine serum albumin (BSA), poly(vinyl alcohol), pluronics, or a naturally occurring surfactant.

129. The method of claim 128, wherein the surfactant is a naturally occurring surfactant.

130. The method of claim 129, wherein the surfactant is a phospholipid.

131. The method of claim 127, wherein the coagulating bath solvent is a non-solvent for the polymer.

132. The method of claim 127, wherein the polymer is at least one polymer selected from the group consisting of poly(L-lactic acid), poly(DL-lactic acid), poly(glycolic acid), polycaprolactone, and polyanhydride.

133. The method of claim 132, wherein the polymer is a copolymer or blend of the polymers selected from the group consisting of poly(L-lactic acid), poly(DL-lactic acid), poly(glycolic acid), polycaprolactone, and polyanhydride.

134. The method of claim 127, wherein the polymer solvent is chloroform or methylene chloride.

135. The method of claim 127, wherein the coagulating bath solvent is hexane, an alcohol or acetone.

136. The method of claim 135, wherein the coagulating bath solvent is isopropyl alcohol.

137. The method of claim 121, wherein the polymer solvent comprises a mixture of at least one good solvent for the polymer and at least one bad solvent for the polymer.

138. The method of claim 137, wherein the at least one good solvent is chloroform or methylene chloride and the at least one bad solvent is toluene.

139. The method of claim 127, wherein the coagulating bath solvent further comprises the polymer solvent.

140. The method of claim 139, wherein the coagulating bath solvent further comprises up to about 20% v/v of the polymer solvent.

141. The method of claim 127, wherein the coagulating bath solvent comprises a viscous solvent.

142. The method of claim 141, wherein the viscous solvent is glycerol.

143. The method of claim 142, wherein the glycerol concentration is between about 8% and about 20% v/v.

144. A method of creating drug-releasing fibers, said method comprising obtaining a polymer solution comprising a synthetic biodegradable polymer in a solvent; adding biomolecule **loaded** NIPA gels to the polymer solution; and extruding the polymer solution into a coagulating bath comprising at least one solvent wherein the polymer solvent is substantially immiscible with water and highly miscible with the coagulating bath solvent.

145. The method of claim 144, wherein the polymer is at least one polymer selected from the group consisting of poly(L-lactic acid), poly(DL-lactic acid), poly(glycolic acid), polycaprolactone, and polyanhydride.

146. The method of claim 145, wherein the polymer comprises a copolymer or blend of more than one polymer selected from the group consisting of poly(L-lactic acid), poly(DL-lactic acid), poly(glycolic acid), polycaprolactone and polyanhydride.

147. The method of claim 144, wherein the polymer solvent is chloroform or methylene chloride.

148. The method of claim 144, wherein the coagulating bath solvent is hexane, an alcohol or acetone.

149. The method of claim 148, wherein the coagulating bath solvent is isopropyl alcohol.

150. The method of claim 144, wherein the polymer solvent comprises a mixture of at least one good solvent for the polymer and at least one poor solvent for the polymer.

151. The method of claim 149, wherein the at least one good solvent is chloroform or methylene chloride and the at least one poor solvent is toluene.

152. The method of claim 144, wherein the coagulating bath solvent further comprises the polymer solvent.

153. The method of claim 152, wherein the coagulating bath contains up to 20% v/v of the polymer solvent.

154. The method of claim 144, wherein the coagulating bath solvent comprises a viscous solvent.

155. The method of claim 154, wherein the viscous solvent is glycerol.

156. The method of claim 155, wherein the glycerol concentration is between about 8% and about 20% v/v.

157. A method of creating a drug releasing fiber from chitosan, said method comprising: a) obtaining a polymer solution comprising chitosan and a hydrochloric acid; and b) extruding the polymer solution into a coagulating bath comprising tris base.

158. The method of claim 157, wherein the concentration of the hydrochloric acid is about 1%.

159. The method of claim 157, wherein the concentration of tris base is between about 5% and about 15%.

160. The method of claim 157, further comprising adding microspheres comprising at least one biomolecule to the chitosan solution prior to extruding.

161. The method of claim 160, wherein the biomolecule microsphere is made from a either a pure polymer, or is a copolymer or blend of the polymers selected from the group consisting of poly(L-lactic acid), poly(DL-lactic acid), poly(glycolic acid), polycaprolactone, and polyanhydridepoly(L-lactic acid).

162. The method of claim 145, further comprising applying at least one polymer coating comprising containing a biomolecule emulsion to said fibers thereby rendering said fibers capable of temporally controlling release of said multiple biomolecules, wherein said applying step is prior to the extruding step.

163. The method of claim 162, wherein said applying comprises passing said fiber through a spinneret comprising the emulsion.

164. The method of claim 162, further comprising assembling multiple fibers into a fabric, each wherein one or more fibers of said fabric comprising at least one biomolecule having a specific activity for a certain cell type, wherein said biomolecule may differ from the biomolecule in other fibers in said fabric.

165. The method of claim 164, wherein the fibers release the biomolecules over a period of time.

166. The method of claim 164, wherein at least a portion of the fibers may be coated to release various factors and chemicals over a period of time.

167. The method of claim 164, wherein the biomolecule in at least a portion of the fibers is VEGF.

168. The method of claim 166, wherein a first portion of the coated fibers correspond to a first phase of dermal wound healing, a second portion of the coated fibers correspond to a second phase of dermal wound healing and a third portion of the coated fibers correspond to a third phase of dermal wound healing.

169. The method composition of claim 168, wherein the first portion of coated fibers comprise a coating that induces thrombus formation to achieve rapid homeostasis.

170. The method composition of claim 168, wherein the second portion of coated fibers comprise neutrophil and **macrophage** recruiting agents.

171. The method composition of claim 170, wherein the neutrophil and **macrophage** recruiting agents may be one or more of a compound selected from the group consisting of PDGF, TGF(beta), FGF, IL-1 and TNF.

172. The method composition of claim 164, wherein the fibers induce cells to form a functioning artery.

173. The method composition of claim 172, wherein the fabric comprises induces the formation of an endothelial cell layer, a media layer and an adventitia layer.

174. The method composition of claim 173, wherein the media layer comprises smooth muscle cells that are aligned circumferentially by the winding of the fibers.

175. The method composition of claim 173, wherein the adventitia layer comprises fibroblasts with components of vasa vasorum from longitudinally arranged VEGF fibers.

176. A composition of parallel fibers bundled in a circular cross section for the treatment of lesions in the nervous system wherein at least some of the fibers are **loaded** with a neurotrophin.

177. The composition of claim 176, wherein the lesion is in the peripheral nervous system.

178. The composition of claim 176, wherein the lesion is in the central nervous system.

179. A composition for treating lesions of the digestive system, comprising fibers **loaded** with one or more biomolecule induction of epithelial cells, smooth muscle cells etc., into a tubular shaped scaffold.

180. A composition for treating lesions of the musculoskeletal system, comprising a scaffold comprising fibers in parallel arrays for the induction and alignment of musculoskeletal cells.

181. The composition of claim 180, wherein said scaffold further comprises fibers containing factors that promote angiogenesis.

182. The composition of claim 180, wherein said scaffold further comprises fibers containing neurotrophins.

183. The composition of claim 181, wherein said scaffold further comprises fibers containing neurortrophins.

184. The method of claim 162, wherein said coated fiber is fabricated by coaxial multi-component extrusion techniques.

185. The method of claim 121, wherein the first polymer solution contains an organic soluble active biomolecules(s) that is directly dissolved in the polymer solution and there is no aqueous phase.

186. The method of claim 121, wherein the first polymer solution contains at least one organic soluble active biomolecules that is directly dissolved in the polymer solution and an aqueous emulsion.

187. The method of claim 186, wherein the aqueous emulsion further comprises a water soluble biomolecule and a surfactant.

188. The method of claim 121, wherein the second polymer solution does not contain an emulsion or a surfactant.

189. The composition of claim 19, wherein said scaffold comprises braided fibers.

190. A composition of a coaxial fiber comprising a first segment and a second segment, wherein the first segment comprises an inert sealant and the second segment contains at least one biologically active molecule.

191. The composition of claim 190, wherein the fiber is coated with a

composition comprising at least one biologically active molecule.

192. The composition of claim 1, wherein said scaffold comprises braided fibers.

193. The composition of claim 1, wherein said fibers or a subset of said fibers comprise fibers containing one or more therapeutic agents, wherein the content of said one or more therapeutic agents within said fibers or said subset of fibers varies circumferentially around said fibers or subset of fibers.

194. The composition of claim 1, wherein said the scaffold contains multiple fiber types, wherein the types of fibers differ by the biomolecules that are contained within the fiber.

195. The composition of claim 194 wherein fibers containing different therapeutic agents are distributed non-homogeneously throughout the scaffold.

196. The composition of claim 195, wherein the non-homogeneous distribution of therapeutic agents is patterned to direct biological processes in specific three-dimensional locations throughout the scaffold.

197. The composition of claim 196, wherein the biological process that is directed is cell migration.

198. A composition of fibers that release neurotrophins to the optical nerve when placed near the optical nerve.

L26 ANSWER 42 OF 54 USPATFULL on STN
2003:207289 Anticancer vaccine and diagnostic methods and reagents.
Finn, Olivera J., Pittsburgh, PA, UNITED STATES
Kao, Henry, St. Louis, MO, UNITED STATES
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Marto, Jarrod A., Charlottesville, VA, UNITED STATES
University of Pittsburgh of the Commonwealth System of Higher Education, Pittsburgh, PA, 15260 (U.S. corporation)
US 2003143647 A1 20030731
APPLICATION: US 2002-253867 A1 20020924 (10)
PRIORITY: US 2001-324450P 20010924 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A method for diagnosing a malignant or pre-malignant condition within a patient comprising assaying for the expression of a cyclin molecule within the patient, whereby deregulated cyclin expression supports a diagnosis of a malignant or pre-malignant condition.

2. The method of claim 1, wherein the condition is diagnosed within a biopsy comprising tissue excised from the patient.

3. The method of claim 1, wherein the condition is lung cancer or precancer, breast cancer or precancer, pancreatic cancer or precancer, or colon cancer or precancer.

4. The method of claim 1, wherein the condition is a malignancy or premalignancy associated with altered or absent p53 production.

5. The method of claim 1, wherein the cyclin molecule is cyclin B1.

6. A method for diagnosing a malignant or pre-malignant condition within a patient comprising assaying for immunoreactivity to a cyclin molecule within the patient, whereby the presence of immunoreactivity supports a diagnosis of a malignant or pre-malignant condition.

7. The method of claim 6, where the immunoreactivity is humoral immunoreactivity.

8. The method of claim 6, where the immunoreactivity is cellular immunoreactivity.

9. The method of claim 6, comprising assaying for the serum titer of antibodies specific for a cyclin molecule within the patient, whereby elevated antibody titer expression supports a diagnosis of a malignant or pre-malignant condition.

10. The method of claim 9, wherein the assay is accomplished by ELISA.

11. The method of claim 6, wherein the condition is lung cancer or precancer, breast cancer or precancer, pancreatic cancer or precancer, or colon cancer or precancer.

12. The method of claim 6, wherein the condition is a malignancy or premalignancy associated with altered or absent p53 production.

13. The method of claim 6, wherein the cyclin molecule is cyclin B1.

14. A method for vaccinating a patient against malignancies comprising introducing a peptide consisting essentially of all or an immunogenic fragment of a cyclin protein into a patient under conditions sufficient for the patient to develop an immune response to the cyclin protein.

15. The method of claim 14, wherein the peptide consists essentially of all or an immunogenic fragment of a cyclin A, D1, B1, or E protein.

16. The method of claim 14, wherein the peptide consists essentially of a mature cyclin B1 protein.

17. The method of claim 14, wherein the peptide consists essentially of a fragment of from about 5 to about 15 contiguous amino acids of a wild-type human cyclin B1 peptide and which has from 0 to about 5 single amino acid substitutions relative to the wild-type sequence.

18. The method of claim 14, wherein the peptide comprises an amino acid sequence as set forth in SEQ ID NOs: 1-8.

19. A method of priming T cells against tumor antigens comprising, obtaining naive CD4+ or CD8+ T cells from at least one healthy individual, obtaining at least one protein or peptide from at least one cancerous cell; obtaining antigen presenting cells (APCs), culturing the APCs with the at least one protein or peptide, and adding the T cells to the culture of the APCs, whereby the T cells are primed against the at least one protein or peptide.

20. The method of claim 19, wherein the T cells are CD4+ T cells

21. The method of claim 19, wherein the at least one protein or peptide is obtained by lysing the cancerous cell to obtain a lysate and extracting the protein or peptide from the lysate.

22. The method of claim 19, wherein the T cells are CD8+ T cells.

23. The method of claim 19, wherein the at least one protein or peptide is obtained by extracting HLA class I molecules from the cancerous cell and eluting the protein or peptide from the extracted HLA class I molecules.

24. The method of claim 19, wherein the at least one protein or peptide is fractionated.

25. The method of claim 19, wherein the at least one protein or peptide is obtained from a tumor comprising the at least one cancerous cell.

26. The method of claim 19, wherein the APCs are dendritic cells.

27. The method of claim 26, wherein the dendritic cells are generated in vitro.

28. The method of claim 19, wherein the APCs are cultured with the at least one protein or peptide in the presence of tumor necrosis factor α.

29. The method of claim 19, wherein the T cells are added to the culture of the APCs in the presence of one or more cytokines.

30. The method of claim 29, wherein the cytokines are selected from the group of cytokines consisting of IL-1β, IL-2, and IL-4, and IL-7.

31. The method of claim 19, wherein the T cell/APC culture is restimulated by introducing autologous **macrophages, loaded** with the at least one protein or peptide, or irradiated cancerous cells.

32. The method of claim 19, wherein the T cell/APC culture is restimulated more than one time at intervals of from about 7 to about 10 days.

33. A method of identifying tumor antigens comprising, obtaining naive CD4+ or CD8+ T cells from at least one healthy individual, obtaining at least one protein or peptide from at least one cancerous cell; obtaining antigen presenting cells (APCs), culturing the APCs with the at least one protein or peptide, and adding the T cells to the culture of the APCs, whereby the T cells are primed against the at least one protein or peptide, and assessing the peptide sequence of the stimulatory molecules.

34. The method of claim 33, wherein the T cells are CD4+ T cells

35. The method of claim 33, wherein the at least one protein or peptide is obtained by lysing the cancerous cell to obtain a lysate and extracting the protein or peptide from the lysate.

36. The method of claim 33, wherein the T cells are CD8+ T cells.

37. The method of claim 33, wherein the at least one protein or peptide is obtained by extracting HLA class I molecules from the cancerous cell and eluting the protein or peptide from the extracted HLA class I molecules.

38. The method of claim 33, wherein the at least one protein or peptide is fractionated.

39. The method of claim 33, wherein the at least one protein or peptide is obtained from a tumor comprising the at least one cancerous cell.

40. The method of claim 33, wherein the APCs are dendritic cells.

41. The method of claim 41, wherein the dendritic cells are generated in vitro.

42. The method of claim 33, wherein the APCs are cultured with the at least one protein or peptide in the presence of tumor necrosis factor α.

43. The method of claim 33, wherein the T cells are added to the culture of the APCs in the presence of one or more cytokines.

44. The method of claim 43, wherein the cytokines are selected from the group of cytokines consisting of IL-1β, IL-2, and IL-4, and IL-7.

45. The method of claim 33, wherein the T cell/APC culture is restimulated by introducing autologous **macrophages**, **loaded** with the at least one protein or peptide, or irradiated cancerous cells.

46. The method of claim 33, wherein the T cell/APC culture is restimulated more than one time at intervals of from about 7 to about 10 days.

L26 ANSWER 43 OF 54 USPATFULL on STN
2003:201628 Method of searching for arteriosclerosis inhibitors and shrinkers.
Tozawa, Ryuichi, Osaka, JAPAN
Fuse, Hiromitsu, Tsukuba-shi, JAPAN
Kita, Shunbun, Hyogo, JAPAN
Nakamura, Masahira, Nara, JAPAN
US 2003139616 A1 20030724
APPLICATION: US 2002-258363 A1 20021022 (10)
WO 2001-JP3598 20010426
PRIORITY: JP 2000-129771 20000428
JP 2000-146386 20000518
JP 2000-212836 20000713
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A method of extracting or removing intracellular free cholesterol which comprises selectively extracting or removing free cholesterol from cells with an aqueous alcohol.

2. The extracting or removing method according to claim 1, wherein the alcohol is a polar aliphatic monohydric alcohol having 1 to 4 carbon atoms.

3. The extracting or removing method according to claim 1, wherein the alcohol is methanol.

4. The extracting or removing method according to claim 1, wherein the water content of the aqueous alcohol is 5 to 60 (v/v) %.

5. The extracting or removing method according to claim 1, wherein the aqueous alcohol and cyclodextrin(s) are used.

6. The extracting or removing method according to claim 1, wherein the cells are those derived from a mammal.

7. The extracting or removing method according to claim 1, wherein the cells are peripheral blood-derived **monocyte macrophages** derived from a mammal, peritoneal **macrophages** derived from a mammal, alveolar

macrophages derived from a mammal, aortic **macrophages** derived from a mammal, smooth muscular cells derived from a mammal, fibroblasts derived from a mammal, hepatocytes derived from a mammal, dendritic cell strains derived from a mammal, THP-1 (human), U937 (human), HepG2 (human), J774 (mouse), L-1 (mouse), RAW264.7 (mouse), WEHI (mouse) or P388D1 (mouse).

8. A method of measuring the amount of intracellular cholesteryl esters which comprises selectively extracting and removing free cholesterol from cells with an aqueous alcohol and/or cyclodextrin(s) and then measuring the amount of the intracellular cholesteryl esters.

9. The method according to claim 8, wherein whole lipid is extracted with a solvent from the cells from which free cholesterol has been extracted and removed, and the amount of cholesteryl esters in the whole lipid is quantified by an enzyme method using a cholesterol oxidase, a TLC method or liquid chromatography.

10. The method according to claim 9, wherein the solvent is chloroform-methanol or hexane-isopropanol.

11. The method according to claim 8, wherein the intracellular cholesterol is labeled, free cholesterol is selectively extracted and removed from the cells, and then the amount of the label in the cells is measured.

12. A method of evaluating the regulatory activity of a test substance on the intracellular cholesteryl ester metabolism which comprises the procedure of selectively extracting free cholesterol from cells with an aqueous alcohol.

13. The evaluation method according to claim 12, wherein (i) the cells are **loaded** with cholesterol or a cholesteryl ester, or (ii) a cholesteryl ester are formed in the cells to allow the cells to become foam cells.

14. The evaluation method according to claim 13, wherein the loading of cells with cholesterol or a cholesteryl ester is carried out by addition of (i) a solution of cholesterol or a cholesteryl ester in an alcohol or (ii) a complex of cholesterol or a cholesteryl ester and lipoprotein.

15. The evaluation method according to claim 14, wherein the lipoprotein is LDL, acetyl LDL, oxidized LDL, glycated LDL or β-VLDL.

16. The evaluation method according to claim 13, wherein the formation of the cholesteryl ester in the cells is carried out by addition of oxysterols, lipoprotein, cholesterol-containing liposome or cytokine.

17. The evaluation method according to claim 16, wherein the oxysterol is 25-hydroxycholesterol or 7-ketocholesterol.

18. The evaluation method according to claim 16, wherein the lipoprotein is LDL, acetyl LDL, oxidized LDL, glycated LDL or β-VLDL.

19. The evaluation method according to claim 16, wherein the cytokine is interferon γ.

20. The evaluation method according to claim 12, wherein the alcohol is a polar aliphatic monohydric alcohol having 1 to 4 carbon atoms.

21. The evaluation method according to claim 12, wherein the alcohol is methanol.

22. The evaluation method according to claim 12, wherein the water content of the aqueous alcohol is 5 to 60 (v/v) %.

23. The evaluation method according to claim 12, wherein the cells are those derived from a mammal.

24. The evaluation method according to claim 12, wherein the cells are peripheral blood-derived **monocyte macrophages** derived from a mammal, peritoneal **macrophages** derived from a mammal, alveolar **macrophages** derived from a mammal, aortic **macrophages** derived from a mammal, smooth muscular cells derived from a mammal, fibroblasts derived from a mammal, hepatocytes derived from a mammal, dendritic cell strains derived from a mammal, THP-1 (human), U937 (human), HepG2 (human), J774 (mouse), L-1 (mouse), RAW264.7 (mouse), WEHI (mouse) or P388D1 (mouse).

25. The evaluation method according to claim 12, wherein free cholesterol is selectively extracted with an aqueous alcohol from cells cultured in the presence of a test substance and cells cultured in the absence of the test substance, and then the amounts of intracellular cholesteryl esters in respective cells cultured in the presence of and in the absence of the test substance are measured and compared to each other.

26. The evaluation method according to any one of claims 12 to 25, wherein the regulation of the intracellular cholesteryl ester metabolism is regulation of an activity of forming intracellular cholesteryl esters.

27. The evaluation method according to any one of claims 12 to 25, wherein the regulation of the intracellular cholesteryl ester metabolism is regulation of an activity of hydrolysis of intracellular cholesteryl esters.

28. The evaluation method according to any of claims 12 to 25 which is a method of screening a compound having an activity of regulating the intracellular cholesteryl ester metabolism.

29. The evaluation method according to claim 28 which is a method of screening a compound having an inhibitory activity on formation of intracellular cholesteryl esters.

30. The evaluation method according to claim 28 which is a method of screening a compound having a promoting activity on hydrolysis of intracellular cholesteryl esters.

31. The evaluation method according to claim 28 which is a method of screening a compound having a defoaming activity.

32. A compound having a regulatory activity on the intracellular cholesteryl ester metabolism selected by the method according to claim 28, or a salt thereof.

33. A defoaming stimulator which comprises as an active ingredient a compound having a regulatory activity on the intracellular cholesteryl ester metabolism selected by the method according to claim 28, or a pharmaceutically acceptable salt thereof.

34. Antiatherogenic agents or regression agents of atherosclerotic lesion which comprises as an active ingredient a compound having a regulatory activity on the intracellular cholesteryl ester metabolism selected by the method according to claim 28, or a pharmaceutically acceptable salt thereof.

35. A method of stimulating defoaming which comprises administering an effective amount of a compound having a regulatory activity on the intracellular cholesteryl ester metabolism selected by the method according to claim 28, or a salt thereof to a mammal.

36. A method of preventing and treating atherosclerosis which comprises administering an effective amount of a compound having a regulatory activity on the intracellular cholesteryl ester metabolism selected by the method according to claim 28, or a salt thereof to a mammal.

37. Use of a compound having a regulatory activity on the intracellular cholesteryl ester metabolism selected by the method according to claim 28, or a salt thereof for the manufacture of a defoaming stimulator.

38. Use of a compound having a regulatory activity on the intracellular cholesteryl ester metabolism selected by the method according to claim 28, or a salt thereof for the manufacture of an agent for preventing and treating atherosclerosis.

39. Use of an aqueous alcohol for selectively extracting or removing free cholesterol from cells.

L26 ANSWER 44 OF 54 USPATFULL on STN
2003:134092 Method for generating highly active human dendritic cells from monocytes.
Belardelli, Filippo, Roma, ITALY
Santini, Stefano Maria, Roma, ITALY
Parlato, Stefania, Roma, ITALY
Pucchio, Tiziana Di, Isola del Liri, ITALY
Logozzi, Mariantonia, Roma, ITALY
Lapenta, Caterina, Firenze, ITALY
Ferrantini, Maria, Roma, ITALY
Santodonato, Laura, Roma, ITALY
D'Agostino, Giuseppina, Roma, ITALY
US 2003092177 A1 20030515
APPLICATION: US 2001-845042 A1 20010427 (9)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A process for deriving dendritic cells from mononuclear cells in culture, wherein said cells are peripheral blood mononuclear cells (PBMC) or CD14+ **monocytes**, comprising the step of putting in contact said mononuclear cells with type I interferon (IFN) at a final concentration greater than 100 IU/ml, since the initial culture thereof.

2. The process according to claim 1, wherein said step is carried out within 3 days of culture.

3. The process according to claim 1, wherein said type I IFN used is selected from the group consisting of any natural IFNα, any recombinant species of IFNα, natural or recombinant IFNβ and any synthetic type I IFN.

4. The process according to claim 2, wherein said type I IFN used is selected from the group consisting of any natural IFNα, any recombinant species of IFNα, natural or recombinant IFNβ and any synthetic type I IFN.

5. The process according to claim 1, wherein said final concentration is in a range of 100-10,000 IU/ml.

6. The process according to claim 2, wherein said final concentration is in a range of 100-10,000 IU/ml.

7. The process according to claim 5, wherein said final concentration is in a range of 400-10,000 IU/ml.

8. The process according to claim 6, wherein said final concentration is in a range of 400-10,000 IU/ml.

9. The process according to claim 7, wherein said final concentration is in a range of 500-2,000 IU/ml.

10. The process according to claim 8, wherein said final concentration is in a range of 500-2,000 IU/ml.

11. The process according to claim 9, wherein said final concentration is 1,000 IU/ml.

12. The process according to claim 10, wherein said final concentration is 1,000 IU/ml.

13. The process according to claim 1, wherein said step is carried out in presence of a cell growth factor.

14. The process according to claim 2, wherein said step is carried out in presence of a cell growth factor.

15. The process according to claim 13, wherein said growth factor is GM-CSF.

16. The process according to claim 14, wherein said growth factor is GM-CSF.

17. The process according to claim 15, wherein said GM-CSF is used at a concentration in a range of 250-1,000 U/ml.

18. The process according to claim 16, wherein said GM-CSF is used at a concentration in a range of 250-1,000 U/ml.

19. The process according to claim 1, wherein said process further includes the step of putting in contact dendritic cells, obtained by treating mononuclear cells with type I IFN, with a maturation agent.

20. The process according to claim 2, wherein said process further includes the step of putting in contact dendritic cells, obtained by treating mononuclear cells with type I IFN, with a maturation agent.

21. The method of use of type I IFN as an agent allowing the ex vivo derivation of dendritic cells from mononuclear cells, the type I IFN being put in contact with said mononuclear cells, since the initial culture thereof and at a final concentration greater than 100 IU/ml.

22. The method of use according to claim 21, wherein said type I IFN is used in combination with a cell growth factor which can be GM-CSF.

23. The method of use according to claim 22, wherein said type I IFN concentration is in a range of 100-10,000 IU/ml.

24. The method of use according to claim 23, wherein said type I IFN concentration is in a range of 500-2,000 IU/ml.

25. The method of use according to claim 24, wherein said type I IFN concentration is 1,000 IU/ml.

26. Dendritic cells obtainable by the process according to claim 1.

27. Dendritic cells obtainable by the process according to claim 2.

28. The dendritic cells according to claim 26, said cells being **loaded** with antigenic peptides or proteins, or with a cellular extract containing at least one antigen, or with nucleic acids.

29. The dendritic cells according to claim 27, said cells being **loaded** with antigenic peptides or proteins, or with a cellular extract containing at least one antigen, or with nucleic acids.

30. A kit for deriving a dendritic cell from a mononuclear cell in culture, comprising the elements necessary for the culture and the washings, including bag(s), connecting tube(s), a composition comprising type I IFN and compatible additives, a composition comprising a cell growth factor and compatible additives, and a culture medium, for simultaneous, separate or sequential use in the process according to claim 1.

31. A kit for deriving a dendritic cell from a mononuclear cell in culture, comprising the elements necessary for the culture and the washings, including bag(s), connecting tube(s), a composition comprising type I IFN and compatible additives, a composition comprising a cell growth factor and compatible additives, and a culture medium, for simultaneous, separate or sequential use in the process according to claim 2.

32. A pharmaceutical composition comprising, as an active principle, the dendritic cells according to claim 1, together with a pharmaceutically acceptable carrier vehicle or auxiliary agent.

33. A pharmaceutical composition comprising, as an active principle, the dendritic cells according to claim 2, together with a pharmaceutically acceptable carrier vehicle or auxiliary agent.

34. A vaccine, comprising, as an active principle, the dendritic cells according to claim 1.

35. A vaccine, comprising, as an active principle, the dendritic cells according to claim 2.

36. A vaccine comprising, as an adjuvant, the dendritic cells according to claim 1 together with an immunogen and a pharmaceutically acceptable carrier vehicle or auxiliary agent.

37. A vaccine comprising, as an adjuvant, the dendritic cells according to claim 2 together with an immunogen and a pharmaceutically acceptable carrier vehicle or auxiliary agent.

38. A method for the treatment of a pathology associated with the presence of an antigen in the human body comprising the step of administering a pharmaceutical composition according to claim 32 to a subject in need thereof.

39. A method for the treatment of a pathology associated with the presence of an antigen in the human body comprising the step of administering a pharmaceutical composition according to claim 33 to a subject in need thereof.

40. A method for the treatment of a pathology associated with the presence of an antigen in the human body comprising the step of administering a vaccine according to claim 34 to a subject in need thereof.

41. A method for the treatment of a pathology associated with the presence of an antigen in the human body comprising the step of administering a vaccine according to claim 35 to a subject in need thereof.

42. A method for the treatment of a pathology associated with the presence of an antigen in the human body comprising the step of administering a vaccine according to claim 36 to a subject in need thereof.

43. A method for the treatment of a pathology associated with the presence of an antigen in the human body comprising the step of administering a vaccine according to claim 37 to a subject in need thereof.

44. A method according to claim 40, wherein said pathology is an infection or a neoplastic disease.

45. A method according to claim 41, wherein said pathology is an infection or a neoplastic disease.

46. A method according to claim 42, wherein said pathology is an infection or a neoplastic disease.

47. A method according to claim 43, wherein said pathology is an infection or a neoplastic disease.

48. A method according to claim 38, wherein administration is located at the site of the infection or within the primary tumor.

49. A method according to claim 39, wherein administration is located at the site of the infection or within the primary tumor.

50. A method for the ex vivo expansion of T cells to be reinfused in a subject in need thereof, comprising the step of putting in contact said T cells with the dendritic cells according to claim 26.

51. A method for the ex vivo expansion of T cells to be reinfused in a subject in need thereof, comprising the step of putting in contact said T cells with the dendritic cells according to claim 27.

52. A method for the ex vivo expansion of T cells to be reinfused in a subject in need thereof, comprising the step of putting in contact said T cells with the dendritic cells according to claim 28.

53. A method for the ex vivo expansion of T cells to be reinfused in a subject in need thereof, comprising the step of putting in contact said T cells with the dendritic cells according to claim 29.

L26 ANSWER 45 OF 54 USPATFULL on STN
2003:120325 Maturation of antigen-presenting cells using activated T cells.
Berenson, Ronald Jay, Mercer Island, WA, UNITED STATES
Bonyhadi, Mark, Issaquah, WA, UNITED STATES
Craig, Stewart, Issaquah, WA, UNITED STATES
Kalamasz, Dale, Redmond, WA, UNITED STATES

Monji, Tatsue, Seattle, WA, UNITED STATES
XCYTE Therapies, Inc., Seattle, WA (U.S. corporation)
US 2003082806 A1 20030501
APPLICATION: US 2002-136024 A1 20020429 (10)
PRIORITY: US 2001-287168P 20010427 (60)
US 2001-295331P 20010601 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A method for maturing dendritic cells, comprising: (a) providing a population of cells wherein at least a portion thereof comprises immature dendritic cells; and (b) exposing the population of cells to activated T cells or supernatant therefrom, thereby inducing maturation.

2. The method of claim 1 wherein the immature dendritic cells are generated from a source of precursor cells selected from the group consisting of leukapheresis product, peripheral blood, lymph node, skin, GALT, tonsil, thymus, tissue biopsy, tumor, spleen, skin, bone marrow, cord blood, CD34+ cells, **monocytes**, and adherent cells.

3. The method of claim 2 wherein the immature dendritic cells are generated by exposing the precursor cells to activated T cells or supernatant therefrom.

4. The method of claim 1 wherein the immature dendritic cells comprise dendritic/tumor cell fusions.

5. The method of claim 4 wherein the tumor cells used to generate the dendritic/tumor cell fusions are from a cancer.

6. The method of claim 5 wherein the cancer is selected from the group consisting of

7. The method of claim 1 wherein the immature dendritic cells are generated from a source of precursor cells selected from the group consisting of leukapheresis product, peripheral blood, lymph node, skin, GALT, tonsil, thymus, tissue biopsy, tumor, spleen, bone marrow, cord blood, CD34+ cells, **monocytes**, and adherent cells by exposing said precursor cells to one or more cytokines.

8. The method of claim 7 wherein the cytokines comprise GM-CSF.

9. The method of claim 7 wherein the cytokines comprise IL-4.

10. The method of claim 7 wherein the cytokines comprise GM-CSF and IL-4.

11. The method of claim 7 wherein the cytokines comprise IL-13.

12. The method of claim 7 wherein the cytokines comprise GM-CSF and IL-13.

13. The method of claim 7 wherein the source of precursor cells comprises leukapheresis product.

14. The method of claim 7 wherein the source of precursor cells comprises peripheral blood.

15. The method of claim 7 wherein the source of precursor cells comprises bone marrow.

16. The method of claim 7 wherein the source of precursor cells

comprises cord blood.

17. The method of claim 7 wherein the source of precursor cells comprises CD34+ cells.

18. The method of claim 7 wherein the source of precursor cells comprises **monocytes**.

19. The method of claim 7 wherein the source of precursor cells comprises adherent cells.

20. The method of claim 1 wherein the immature dendritic cells are generated from a source of precursor cells selected from the group consisting of leukapheresis product, peripheral blood, lymph node, skin, GALT, tonsil, thymus, tissue biopsy, tumor, spleen, skin, bone marrow, cord blood, CD34+ cells, **monocytes**, and adherent cells by exposing said precursor cells to one or more cytokines and activated T cells or supernatant therefrom.

21. The method according to claim 1 wherein the immature dendritic cells are **loaded** with antigen through gene modification or by exposing the immature dendritic cells to a source of antigen selected from the group consisting of protein, peptides, tumor lysate, and apoptotic bodies.

22. The method according to claim 21 wherein the source of antigen comprises protein.

23. The method according to claim 21 wherein the source of antigen comprises peptides and/or polypeptides

24. The method according to claim 21 wherein the source of antigen comprises tumor lysates.

25. The method according to claim 21 wherein the source of antigen comprises apoptotic bodies.

26. The method according to claim 21 wherein the source of antigen comprises irradiated tumor cells from a tumor or a cell line.

27. The method according to claim 1 wherein the dendritic cells are genetically modified.

28. The method of claim 1 wherein the activated T cells comprise a T cell line.

29. The method of claim 1 wherein the activated T cells are generated by cell surface moiety ligation comprising: (a) providing a population of cells wherein at least a portion thereof comprises T cells; and (b) exposing the population of cells to an agent that induces activation of said T cells.

30. The method of claim 29 wherein the agent comprises anti-T cell receptor antibodies.

31. The method of claim 29 wherein the agent comprises anti-CD3 antibodies.

32. The method of claim 29 wherein the agent comprises anti-CD28 antibodies.

33. The method of claim 29 wherein the agent comprises anti-CD3 and anti-CD28 antibodies.

34. The method of claim 1 wherein the activated T cells are generated by simultaneous T cell concentration and cell surface moiety ligation, comprising: (a) providing a population of cells wherein at least a portion thereof comprises T cells; (b) exposing the population of cells to a surface, wherein the surface has attached thereto one or more agents that ligate a cell surface moiety of at least a portion of the T cells and stimulates at least a portion of T cells. (c) applying a force that predominantly drives T cell concentration and T cell surface moiety ligation, thereby inducing T cell stimulation.

35. A population of mature dendritic cells generated according to the method of claim 1.

36. A population of mature dendritic cells according to claim 35 wherein the dendritic cells are fused to tumor cells to form dendritic/tumor cell fusions.

37. A composition comprising the dendritic/tumor cell fusions according to claim 36 and a pharmaceutically acceptable excipient.

38. A method for stimulating an immune response in a mammal comprising, administering to the mammal the composition of claim 37.

39. A method for reducing the presence of cancer cells in a mammal comprising, exposing the cells to the composition of claim 37.

40. A method for inhibiting the development of a cancer in a mammal, comprising administering to the mammal the composition of claim 37.

41. A composition comprising the dendritic cells according to claim 35 and a pharmaceutically acceptable excipient.

42. A composition according to claim 41 wherein the dendritic cells are genetically modified.

43. A method for stimulating an immune response in a mammal comprising, administering to the mammal the composition of claim 41.

44. The method of claim 43 wherein the immune response comprises the activation of T cells in the mammal.

45. A method for ameliorating an immune response dysfunction in a mammal comprising administering to the mammal the composition of claim 41.

46. A method for reducing the presence of cancer cells in a mammal comprising, exposing the cells to the composition of claim 41.

47. The method of claim 46 wherein the cancer cells are from a cancer selected from the group consisting of melanoma, non-Hodgkin's lymphoma, Hodgkin's disease, leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, and chronic lymphocytic leukemia.

48. The method of claim 46 wherein the cancer comprises leukemia.

49. A method for reducing the presence of an infectious organism in a mammal comprising, administering to the mammal the composition of claim 41.

50. A method for inhibiting the development of a cancer in a mammal, comprising administering to the mammal the composition of claim 41.

51. The method of claim 50 wherein the cancer is selected from the group consisting of melanoma, non-Hodgkin's lymphoma, Hodgkin's disease, leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, and chronic lymphocytic leukemia.

52. The method of claim 50 wherein the cancer comprises leukemia.

53. A method for inhibiting the development of an infectious disease in a mammal, comprising administering to the mammal the composition of claim 41.

54. A composition comprising dendritic cells and activated T cells wherein the dendritic cells have been matured by exposure to activated T cells or supernatant therefrom ex vivo.

55. The composition of claim 54, further comprising a pharmaceutically acceptable excipient.

56. A method for stimulating an immune response in a mammal, comprising administering to the mammal the composition of claim 55.

57. A method for inhibiting the development of a cancer in a mammal, comprising administering to the mammal the composition of claim 55.

58. The method of claim 57 wherein the cancer is selected from the group consisting of melanoma, non-Hodgkin's lymphoma, Hodgkin's disease, leukemia, plasmocytoma, sarcoma, glioma, thymoma, breast cancer, prostate cancer, colo-rectal cancer, kidney cancer, renal cell carcinoma, pancreatic cancer, esophageal cancer, brain cancer, lung cancer, ovarian cancer, cervical cancer, multiple myeloma, hepatomocellular carcinoma, acute lymphoblastic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, and chronic lymphocytic leukemia.

59. The method of claim 57 wherein the cancer comprises leukemia.

60. A method for inhibiting the development of an infectious disease in a mammal, comprising administering to the mammal the composition of claim 55.

61. A method for reducing the presence of cancer cells in a mammal, comprising administering to the mammal a composition comprising, dendritic cells matured by activated T cells or supernatant therefrom ex vivo, activated T cells, and a pharmaceutically acceptable excipient.

62. The method of claim 61 wherein the cancer cells are selected from the group consisting of a melanoma, non-Hodgkin's lymphoma, Hodgkin's disease, leukemia, plasmocytoma, sarcoma, glioma, thymoma, breast cancer, prostate cancer, colo-rectal cancer, kidney cancer, renal cell carcinoma, pancreatic cancer, esophageal cancer, brain cancer, lung cancer, ovarian cancer, cervical cancer, multiple myeloma, hepatocellular carcinoma, acute lymphoblastic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, and chronic lymphocytic leukemia.

63. The method of claim 61 wherein the cancer cells comprise leukemia.

64. A method for generating mature dendritic cells in vivo comprising, administering to a mammal a composition comprising activated T cells.

65. A method for generating mature dendritic cells, comprising: (a)

generating immature dendritic cells in vitro from a source of precursor cells by a method selected from the group consisting of: i. exposing the precursor cells to GM-CSF and IL-4; ii. exposing the precursor cells to GM-CSF and IL-13; iii. exposing the precursor cells to activated T cells or supernatant therefrom; iv. exposing the precursor cells to GM-CSF and IL-4 and activated T cells or supernatant therefrom; and v. exposing the precursor cells to GM-CSF and IL-13 and activated T cells or supernatant therefrom; (b) administering to a mammal the immature dendritic cells of part (a), and; (c) administering to the mammal activated T cells, thereby inducing in vivo maturation of the immature dendritic cells.

66. The method of claim 65 wherein the source of precursor cells is selected from the group consisting of leukapheresis product, peripheral blood, lymph node, skin, GALT, tonsil, thymus, tissue biopsy, tumor, spleen, skin, bone marrow, cord blood, CD34+ selected cells, **monocytes**, and adherent cells.

67. The method of claim 65 wherein the source of precursor cells is leukapheresis product.

68. The method of claim 65 wherein the source of precursor cells is peripheral blood.

69. The method of claim 65 wherein the source of precursor cells is bone marrow.

70. The method of claim 65 wherein the source of precursor cells is cord blood.

71. The method of claim 65 wherein the source of precursor cells is CD34+ cells.

72. The method of claim 65 wherein the source of precursor cells is **monocytes**.

73. The method of claim 65 wherein the source of precursor cells is adherent cells.

74. A method for generating mature dendritic cells, comprising: (a) obtaining a population of cells from a mammal wherein at least a portion thereof comprises precursor dendritic cells; (b) exposing said portion of cells in vitro to GM-CSF and IL-4 or IL-13 to generate immature dendritic cells; and (c) exposing said immature dendritic cells in vitro to a population of activated T cells or supernatant therefrom for a sufficient period of time to achieve desired maturation.

75. The method of claim 65 wherein the precursor cells are isolated from peripheral blood.

76. The method of claim 65 wherein the precursor cells are isolated from leukapheresis product.

77. The method of claim 76 wherein the activated T cells are generated by a method comprising, exposing the population of T cells to an anti-CD3 antibody and a ligand which binds an accessory molecule on the surface of the T cells, under conditions appropriate for activation of the T cells.

78. The method of claim 76 wherein said activated T cells are generated by a method comprising: (a) exposing the population of T cells to an anti-CD3 antibody which is immobilized on a solid phase surface; and;

(b) stimulating an accessory molecule on the surface of the T cells with an anti-CD28 antibody, wherein said anti-CD28 antibody is immobilized on the same solid phase surface as the anti-CD3 antibody, thereby inducing activation and proliferation of the T cells.

79. The method of claim 78 wherein the activated T cells generated comprise T cells that have proliferated.

80. The method of claim 78 wherein the activated T cells generated comprise T cells that secrete cytokines.

81. A method for expanding dendritic/tumor cell fusions comprising exposing the dendritic/tumor cell fusions to activated T cells or supernatant therefrom.

L26 ANSWER 46 OF 54 USPATFULL on STN
2003:85823 Method for inducing selectively suppressed immune response to transplanted tissue or cells.
Edelson, Richard Leslie, Westport, CT, UNITED STATES
US 2003059426 A1 20030327
APPLICATION: US 2002-217856 A1 20020813 (10)
PRIORITY: US 2001-312004P 20010813 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CLM What is claimed is:
1. A method for selectively suppressing the immune response of an individual to transplanted organs or tissue, comprising the steps of: (a) removing a piece of skin from the donor of an organ or tissue to be transplanted; (b) allografting the piece of skin from the donor to the intended recipient of the organ or tissue to be transplanted; (c) monitoring the intended recipient to determine when an immunological response to the allografted skin occurs in the intended recipient; (d) treating an extracorporeal quantity of blood from the recipient to induce at least one of apoptosis or necrosis of T cells present in the extracorporeal quantity of blood; (e) treating the extracorporeal quantity of blood from the recipient by flowing the blood through an apparatus having plastic channels with a diameter of about 1 mm or less; (f) incubating the treated extracorporeal quantity of blood; and (g) administering the incubated extracorporeal quantity of blood to the intended transplant recipient.

2. The method of claim 1, wherein apoptosis of T cells in the extracorporeal quantity of blood is induced by adding a photoactivatable agent to the extracorporeal quantity of blood, and irradiating the extracorporeal quantity of blood.

3. The method of claim 2, wherein the photoactivatable agent is 8-MOP.

4. The method of claim 1, wherein the apoptosis or necrosis of T cells in the extracorporeal quantity of blood is induced by treatment selected from the group consisting of heat shock, cold shock, ultraviolet energy, x-ray irradiation, gamma irradiation, hydrostatic pressure and hypotonic solutions.

5. The method of claim 1, wherein the treated extracorporeal quantity of blood is incubated for a period of from about 6 to about 48 hours.

6. The method of claim 5, wherein the extracorporeal quantity of blood is incubated for a period of from about 12 to about 24 hours.

7. The method of claim 1, wherein prior to step (d) the method further comprises the step of: separating the **monocytes** and T-cells from at

least one extracorporeal quantity of the recipient's blood by subjecting the blood to a leukapheresis process.

8. The method of claim 2, wherein the steps of irradiating the extracorporeal quantity of blood and of treating the extracorporeal quantity of blood by flowing the blood through an apparatus having plastic channels are performed in a Photopheresis apparatus.

9. The method of claim 1, wherein the extracorporeal quantity of blood is treated by flowing the blood through an apparatus having plastic channels with a diameter of about 1 mm or less.

10. The method of claim 1, further comprising the steps of: (h) obtaining cells from the donor; (i) treating the cells from the donor to render the cells at least one of apoptotic or necrotic; and (j) combining the treated cells from the donor with the extracorporeal quantity of blood from the recipient prior to incubation of the treated extracorporeal quantity of blood.

11. The method of claim 10, wherein the cells obtained from the donor are blood leukocytes.

12. A method for selectively suppressing the immune response of an individual receiving a transplantation of bone marrow or stem cells, comprising the steps of: (a) removing a piece of skin from each of the two biological parents of the intended recipient of the bone marrow or stem cell transplantation; (b) allografting the skin from each of the biological parents to the donor of the bone marrow or stem cells to be transplanted; (c) monitoring the donor to determine when an immunological response to the allografted skin occurs in the donor; (d) treating an extracorporeal quantity of blood from the donor to induce at least one of apoptosis or necrosis of T cells present in the extracorporeal quantity of blood; (f) treating the extracorporeal quantity of blood from the donor by flowing the blood through an apparatus having plastic channels; (g) incubating the extracorporeal quantity of blood; and (h) administering the extracorporeal quantity of blood to the intended transplant recipient.

13. The method of claim 12, wherein apoptosis of T cells in the extracorporeal quantity of blood is induced by adding a photoactivatable agent to the extracorporeal quantity of blood, and irradiating the extracorporeal quantity of blood.

14. The method of claim 13, wherein the photoactivatable agent is 8-MOP.

15. The method of claim 12, wherein the apoptosis or necrosis of T cells in the extracorporeal quantity of blood is induced by treating the blood using a treatment selected from the group consisting of heat shock, ultraviolet radiation, cold shock, x-ray irradiation, gamma irradiation, hydrostatic pressure and hypotonic solutions.

16. The method of claim 12, wherein the extracorporeal quantity of blood is incubated for a period of from about 6 to about 48 hours.

17. The method of claim 16, wherein the extracorporeal quantity of blood is incubated for a period of from about 12 to about 24 hours.

18. The method of claim 12, wherein prior to step (d) the method further comprises the step of: separating the **monocytes** and T-cells from the extracorporeal quantity of the donor's blood by subjecting the blood to a leukapheresis process.

19. The method of claim 13, wherein the steps of irradiating the extracorporeal quantity of blood and of treating the extracorporeal quantity of blood by flowing the blood through an apparatus having plastic channels are performed in a Photopheresis apparatus.

20. The method of claim 12, wherein the extracorporeal quantity of blood is treated by flowing the blood through an apparatus having plastic channels with a diameter of about 1 mm or less.

21. A method for selectively suppressing the immune response of an individual to transplanted organs or tissue, comprising the steps of: (a) removing a piece of skin from the donor of an organ or tissue to be transplanted; (b) allografting the piece of skin from the donor to the intended recipient of the organ or tissue to be transplanted; (c) monitoring the intended recipient to determine when an immunological response to the allografted skin occurs in the intended recipient; (d) treating a first extracorporeal quantity of blood from the recipient to induce at least one of apoptosis or necrosis of T cells present in the extracorporeal quantity of blood; (e) treating a second extracorporeal quantity of blood from the recipient by flowing the blood through an apparatus having plastic channels with a diameter of about 1 mm or less; (f) combining the first extracorporeal quantity of blood and the second extracorporeal quantity of blood following treatment; (g) incubating the combined extracorporeal quantity of blood; and (h) administering the incubated extracorporeal quantity of blood to the intended transplant recipient.

22. The method of claim 21, wherein apoptosis of T cells in the first extracorporeal quantity of blood is induced by adding a photoactivatable agent to the first extracorporeal quantity of blood, and irradiating the first extracorporeal quantity of blood.

23. The method of claim 21, wherein the photoactivatable agent is 8-MOP.

24. The method of claim 21, wherein the apoptosis or necrosis of T cells in the first extracorporeal quantity of blood is induced by treating the blood using a treatment selected from the group consisting of heat shock, cold shock, ultraviolet energy, x-ray irradiation, gamma irradiation hydrostatic pressure and hypotonic solutions.

25. The method of claim 21, wherein the combined extracorporeal quantity of blood is incubated for a period of from about 6 to about 48 hours.

26. The method of claim 25, wherein the combined extracorporeal quantity of blood is incubated for a period of from about 12 to about 24 hours.

27. The method of claim 21, wherein prior to step (d) the method further comprises the step of: separating the T cells and the **monocytes** from the first and second extracorporeal quantities of blood by subjecting the blood to a leukapheresis process.

28. The method of claim 21, wherein the second extracorporeal quantity of blood is treated by flowing the blood through an apparatus having plastic channels with a diameter of about 1 mm or less.

29. A method for skin testing a subject to assess the level of anti-tumor immunity achieved in a patient previously treated with dendritic cells **loaded** with tumor antigens, comprising the steps of: (a) preparing an aliquot of dendritic cells **loaded** with tumor antigens; (b) injecting the aliquot of dendritic cells intradermally in an acceptable skin location on the subject; and (c) measuring the amount of induration that occurs at the injection site over a

predetermined period of time.

30. A method for selectively suppressing the immune response of an individual to transplanted organs or tissue, comprising the steps of: (a) treating the cells from the donor of an organ or tissue to be transplanted; (b) treating the cells obtained from the donor to render the cells at least one of apoptotitc or necrotic; (c) treating an extracorporeal quantity of blood from the intended recipient of the organ or tissue to be transplanted by flowing the blood through an apparatus having plastic channels with a diameter of about 1 mm or less (d) combining the treated cells from the donor with the treated extracorporeal quantity of blood from the recipient; (e) incubating the combined treated cells from the donor and the treated extracorporeal quantity of blood from the recipient; (f) administering the combined and incubated treated cells from the donor and treated blood from the recipient to the intended transplant recipient.

30. The method of claim 29, wherein the cells obtained from the donor are blood leukocytes.

31. The method of claim 30, wherein the blood leukocytes are rendered at least one of apoptotic or necrotic by subjecting the blood leukocytes to a treatment selected from the group consisting of heat shock, cold shock, ultraviolet radiation, x-ray irradiation, gamma irradiation, hydrostatic pressure and hypotonic solutions.

32. The method of claim 29, wherein the extracorporeal quantity of blood from the recipient is treated by flowing the blood through a photopheresis apparatus.

L26 ANSWER 47 OF 54 USPATFULL on STN
2002:330415 Virus derived antimicrobial peptides.
Montelaro, Ronald C., Wexford, PA, UNITED STATES
Mietzner, Timothy A., Pittsburgh, PA, UNITED STATES
University of Pittsburgh (U.S. corporation)
US 2002188102 A1 20021212
APPLICATION: US 2002-79075 A1 20020219 (10)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A peptide having an amino acid sequence selected from the group consisting of: RVIRVVQRACRAIRHIVRRIRQGLRRIL (SEQ ID NO:1); RVIRVVQRACRAIRHIVRRLRQGLRRILRVV (SEQ ID NO:2); RWIRVVQRWCRAIRHIWRRIRQGLRRWLRVV (SEQ ID NO:3); RVVRVVRRVVRR (SEQ ID NO:4) RRVVRRVRRVVRRVVRVVRRVVRR (SEQ ID NO:5); VRRVVRRVVRVVRRVVRRVRRVVRRVVRVVRRVVRR (SEQ ID NO:6); RRVVRRVRRVVRRVVRVVRRVVRRVRRVVRRVVRVVRRVVRR (SEQ ID NO:7); RVVRVVRRVVRRVRRVVRRVVRVVRRVVRRVRRVVRRVVRVVRRVVRR (SEQ ID NO:8); RVVRVVRRWVRR (SEQ ID NO:9); RRWVRRVRRVWRRVVRVVRRWVRR (SEQ ID NO:10); VRRVWRRVVRVVRRWVRRVRRVWRRVVRVVRRWVRR (SEQ ID NO:11); and RVVRVVRRWVRRVRRVWRRVVRVVRRWVRRVRRVWRRVVRVVRRWRVV (SEQ ID NO:12).

2. The peptide of claim 1 having the amino acid sequence: RVIRVVQRACRAfRHIVRRIRQGLRRIL (SEQ ID NO:1).

3. A composition comprising the peptide of claim 2 and a carrier.

4. The peptide of claim 1 having the amino acid sequence: RVIRVVQRACRAIRHIVRRFRQGLRRILRVV (SEQ ID NO:2).

5. A composition comprising the peptide of claim 4 and a carrier.

6. The peptide of claim 1 having the amino acid sequence: RWIRVVQRWCRAIRHIWRRIRQGLRRWLRVV (SEQ ID NO:3).

7. A composition comprising the peptide of claim 6 and a carrier.

8. The peptide of claim 1 having the amino acid sequence: RVVRVVRRVVRR (SEQ ID NO:4)

9. A composition comprising the peptide of claim 8 and a carrier.

10. The peptide of claim 1 having the amino acid sequence: RRVVRRVRRVVRRVVRVVPRVVRR (SEQ ID NO:5).

11. A composition comprising the peptide of claim 10 and a carrier.

12. The peptide of claim 1 having the amino acid sequence: VRRVVRRVVRVVRRVVRRVRRVVRRVVRVVRRVVRR (SEQ ID NO:6).

13. A composition comprising the peptide of claim 12 and a carrier.

14. The peptide of claim 1 having the amino acid sequence: RRVVRRVRRVVRRVVRVVRRVVRRVRRVVRRVVRVVRRVVRR (SEQ ID NO:7);

15. A composition comprising the peptide of claim 14 and a carrier.

16. The peptide of claim 1 having the amino acid sequence: RVVRVVRRVVRRVRRVVRRVVRVVRRVVRRVRRVVRRVVRVVRRVVRR (SEQ ID NO:8).

17. A composition comprising the peptide of claim 16 and a carrier.

18. The peptide of claim 1 having the amino acid sequence: RVVRVVRRWVRR (SEQ ID NO:9).

19. A composition comprising the peptide of claim 18 and a carrier.

20. The peptide of claim 1 having the amino acid sequence: RRWVRRVRRVWRRVVRVVRRWVRR (SEQ ID NO:10).

21. A composition comprising the peptide of claim 20 and a carrier.

22. The peptide of claim 1 having the amino acid sequence: VRRVWRRVVRVVRRWVRRVRRVWRRVVRVVRRWVRR (SEQ ID NO:11);

23. A composition comprising the peptide of claim 23 and a carrier.

24. The peptide of claim 1 having the amino acid sequence: RVVRVVRRWVRRVRRVWRRVVRVVRRWVRRVRRVWRRVVRVVRRWRVV (SEQ ID NO:12).

25. A composition comprising the peptide of claim 24 and a carrier.

26. The peptide of claim 1 wherein said peptide has antimicrobial activity.

27. The peptide of claim 1 wherein said peptide has antimicrobial activity in low salt.

28. The peptide of claim 1 wherein said peptide has antimicrobial activity in physiologic salt.

29. An LLP-1 peptide analog wherein said peptide is modified to optimize amphipathicity.

30. An LLP-1 peptide analog, said peptide comprising an arginine residue on said peptide's charged face, wherein said arginine residue is substituted with another amino acid residue and wherein said peptide analog comprises an amphipathic α-helical structure.

31. An LLP-1 peptide analog, said peptide comprising a tryptophan residue on said peptide's hydrophobic face, wherein said tryptophan residue is substituted with another amino acid residue and wherein said peptide analog comprises an amphipathic α-helical structure.

32. An LLP-1 peptide analog, said peptide comprising a valine residue on said peptide's hydrophobic face, wherein said valine residue is substituted with another amino acid residue and wherein said peptide analog comprises an amphipathic α-helical structure.

33. An LLP-1 peptide analog, said peptide comprising a tryptophan residue and a valine residue on said peptide's hydrophobic face, wherein said tryptophan residue and said valine residue is substituted with another amino acid residue and wherein said peptide analog comprises an amphipathic α-helical structure.

34. An LLP-1 peptide analog, said peptide comprising additional residues to increase its length, wherein said peptide analog comprises an amphipathic α-helical structure.

35. A solid phase substrate comprising at least one peptide selected from the group consisting of: RVIRVVQRACRAIRHIVRRIRQGLRRIL (SEQ ID NO:1); RVIRVVQRACRAIRHIVRRIRQGLRRILRVV (SEQ ID NO:2); RWIRVVQRWCRATRHIWRRIRQGLRRWLRVV (SEQ ID NO:3); RVVRVVRRVVRR (SEQ ID NO:4;) RRVVRRVRRVVRRVVRVVRRVVRR (SEQ ID NO:5); VRRVVRRVVRVVRRVVRRVRRVVRRVVRVVRRVVRR (SEQ ID NO:6); RRVVRRVRRVVRRVVRVVRRVVRRVRRVVRRVVRVVRRVVRR (SEQ ID NO:7); RVVRVVRRVVRRVRRVVRRVVRVVRRVVRRVRRVVRRVVRVVRRVVRR (SEQ ID NO:8); RVVRVVRRWVRR (SEQ ID NO:9); RRWVRRVRRVWRRVVRVVRRWVRR (SEQ ID NO:10); VRRVWRRVVRVVRRWVRRVRRVWRRVVRVVRRWVRR (SEQ ID NO:11); and RVVRVVRRWVRRVRRVWRRVVRVVRRWVRRVRRVWRRVVRVVRRWRVV (SEQ ID NO:12).

36. The solid phase substrate of claim 35 wherein said solid phase substrate is a prosthetic device.

37. The solid phase substrate of claim 35 wherein the prosthetic device is a prosthetic joint.

38. The peptide of claim 1, said peptide comprising at least one cysteine residue.

39. The peptide of claim 39 wherein said peptide is a disulfide linked dimeric peptide.

40. A peptide-**cargo** complex comprising a **cargo** and a peptide selected from the group consisting of: RVIRVVQRACRAIRHIVRRIRQGLRRIL (SEQ ID NO:1); RVIRVVQRACRAIRHIVRRLRQGLRRILRVV (SEQ ID NO:2); RWIRVVQRWCRAIRHIWRRIRQGLRRWLRVV (SEQ ID NO:3); RVVRVVRRVVRR (SEQ ID NO:4); RRVVRRVRRVVRRVVRVVRRVVRR (SEQ ID NO:5); VRRVVRRVVRVVRRVVRRVRRVVRRVVRVVRRVVRR (SEQ ID NO:6); RRVVRRVRRVVRRVVRVVRRVVRRVRRVVRRVVRVVRRVVRR (SEQ ID NO:7); RVVRVVRRVVRRVRRVVRRVVRVVRRVVRRVRRVVRRVVRVVRRVVRR (SEQ ID NO:8); RVVRVVRRWVRR (SEQ ID NO:9); RRWVRRVRRVWRRVVRVVRRWVRR (SEQ ID NO:10); VRRVWRRVVRVVRRWVRRVRRVWRRVVRVVRRWVRR (SEQ ID NO:11); and RVVRVVRRWVRRVRRVWRRVVRVVRRWVRRVRRVWRRVVRVVRRWRVV (SEQ ID NO:12).

41. The peptide-**cargo** complex of claim 40 wherein said peptide has antimicrobial activity and said **cargo** increases the antimicrobial activity of said peptide.

42. A method for inhibiting the growth of a microbe comprising administering to a mammalian cell a microbial growth inhibiting effective amount of at least one peptide selected from the group consisting of: RVIRVVQRACRAIRHIVRRFRQGLRRIL (SEQ ID NO:1); RVIRVVQRACRAIRHIVRRIRQGLRRILRVV (SEQ ID NO:2); RWIRVVQRWCRAIRHIWRRIRQGLRRWLRVV (SEQ ID NO:3); RVVRVVRRVVRR (SEQ ID NO:4); RRVVRRVRRVVRRVVRVVRRVVRR (SEQ ID NO:5); VRRVVRRVVRVVRRVVRRVRRVVRRVVRVVRRVVRR (SEQ ID NO:6); RRVVRRVRRVVRRVVRVVRRVVRRVRRVVRRVVRVVRRVVRR (SEQ ID NO:7); RVVRVVRRVVRRVPRRVVRRVVRVVRRVVRRVRRVVRRVVRVVRRVVRR (SEQ ID NO:8); RVVRVVRRWVRR (SEQ ID NO:9); RRWVRRVRRVWRRVVRVVRRWVRR (SEQ ID NO:10); VRRVWRRVVRVVRRWVRRVRRVWRRVVRVVRRWVRR (SEQ ID NO:11); and RVVRVVRRWVRRVRRVWRRVVRVVRRWVRRVRRVWRRVVRVVRRWRVV (SEQ ID NO:12).

43. The method of claim 42 wherein the microbe is selected from the group consisting of bacteria, fungi and virus.

44. The method of claim 43 wherein the virus is an enveloped virus.

45. The method of claim 44 wherein the enveloped virus is selected from the group consisting of retrovirus, herpesvirus, poxvirus, hepadnavirus, baculovirus, orthomyxovirus, paramyxovirus, togavirus. rhabdovirus, bunyavirus and flavivirus.

46. The method of claim 45 wherein the retrovirus is the lentivirus HIV-1.

47. The method of claim 45 wherein the herpes virus is HSV.

48. The method of claims 45, 46 and 47 wherein the mammalian cell is a human cell.

49. The method of claim 48 wherein the mammalian cell is a peripheral blood **monocyte**.

50. The method of claim 42 wherein said peptide inhibits microbial growth in in vitro cell culture.

51. A method for suppressing HIV-1 infectivity comprising contacting a mammalian cell having HIV-1 with an HIV-1 infectivity suppressing effective amount of at least one peptide selected from the group consisting of: RVIRVVQRACRAFRHIVRRIRQGLRRIL (SEQ ID NO:1); RVIRVVQRACRAIRHIVRRfRQGLRRILRVV (SEQ ID NO:2); RWIRVVQRWCRAIRHIWRRTRQGLRRWLRVV (SEQ ID NO:3); RVVRVVRRVVRR (SEQ ID NO:4); RRVVRRVRRVVRRVVRVVRRVVRR (SEQ ID NO:5); VRRVVRRVVRVVRRVVRRVRRVVRRVVRVVRRVVPRR (SEQ ID NO:6); RRVVRRVRRVVRRVVRVVRRVVRRVRRVVRRVVRVVRRVVRR (SEQ ID NO:7); RVVRVVRRVVRRVRRVVRRVVRVVRRVVRRVRRVVRRVVRVVRRVVRR (SEQ ID NO:8); RVVRVVRRWVRR (SEQ ID NO:9); RRWVRRVRRVWRRVVRVVRRWVRR (SEQ ID NO:10); VRRVWRRVVRVVRRWVRRVRRVWRRVVRVVRRWVRR (SEQ ID NO:11); and RVVRVVRRWVRRVRRVWRRVVRVVRRWVRRVRRVWRRVVRVVRRWRVV (SEQ ID NO:12).

52. The method of claim 51 wherein the mammalian cell is a human cell.

53. The method of claim 52 wherein the human cell is a peripheral blood **monocyte**.

54. A method of inhibiting growth of a microbe in a subject comprising

contacting a cell of the subject with a microbial growth inhibiting effective amount of at least one peptide selected from the group consisting of: RVfRVVQRACRAIRHIVRRIRQGLRRIL (SEQ ID NO:1); RVIRVVQRACRAfRHIVRRIRQGLRRILRVV (SEQ ID NO:2); RWIRVVQRWCRAIRHIWRRIRQGLRRWLRVV (SEQ ID NO:3); RVVRVVRRVVRR (SEQ ID NO:4); RRVVRRVRRVVRRVVRVVRRVVRR (SEQ ID NO:5); VRRVVRRVVRVVRRVVRRVRRVVRRVVRVVRRVVRR (SEQ ID NO:6); RRVVRRVRRVVRRVVRVVRRVVRRVRRVVRRVVRVVRRVVRR (SEQ ID NO:7); RVVRVVRRVVRRVRRVVRRVVRVVRRVVRRVRRVVRRVVRVVRRVVRR (SEQ ID NO:8); RVVRVVRRWVRR (SEQ ID NO:9); RRWVRRVRRVWRRVVRVVRRWVRR (SEQ ID NO:10); VRRVWRRVVRVVRRWVRRVRRVWRRVVRVVRRWVRR (SEQ ID NO:11); and RVVRVVRRWVRRVRRVWRRVVRVVRRWVRRVRRVWRRVVRVVRRWRVV (SEQ ID NO:12).

55. The method of claim 54 wherein said peptide is administered enterally or parenterally.

56. The method of claim 42, 51 or 54 wherein said peptide is attached to a solid phase substrate.

57. The method of claim 54 wherein the microbe is selected from the group consisting of bacteria, fungi and virus.

58. The method of claim 57 wherein the virus is selected from the group consisting of retrovirus, herpesvirus, poxvirus, hepadnavirus, baculovirus, orthomyxovirus, paramyxovirus, togavirus. rhabdovirus, bunyavirus and flavivirus.

59. The method of claim 58 wherein the retrovirus is the lentivirus HIV-1.

60. The method of claim 58 wherein the herpesvirus is HSV.

61. The method of claim 59 wherein the cell is a perhipheral blood **monocyte**.

62. The method of claim 42, 51 or 54 wherein said microbe is resistant to antibiotics.

63. A method for suppressing the infectivity of HIV-1 in a subject comprising contacting a cell of the subject with a HIV-1 infectivity suppressing effective amount of at least one peptide selected from the group consisting of: RVIRVVQRACRAIRHIVRRIRQGLRRIL (SEQ ID NO:1); RVIRVVQRACRAIRHIVRRIRQGLRRILRVV (SEQ ID NO:2); RWIRVVQRWCRAIRHIWRRIRQGLRRWLRVV (SEQ ID NO:3); RVVRVVRRVVRR (SEQ ID NO:4); RRVVRRVRRVVRRVVRVVRRVVRR (SEQ ID NO:5); VRRVVRRVVRVVRRVVRRVRRVVRRVVRVVRRVVRR (SEQ ID NO:6); RRVVRRVRRVVRRVVRVVRRVVRRVRRVVRRVVRVVRRVVRR (SEQ ID NO:7); RVVRVVRRVVRRVRRVVRRVVRVVRRVVRRVRRVVRRVVRVVRRVVRR (SEQ ID NO:8); RVVRVVRRWVRR (SEQ ID NO:9); RRWVRRVRRVWRRVVRVVRRWVRR (SEQ ID NO:10); VRRVWRRVVRVVRRWVRRVRRVWRRVVRVVRRWVRR (SEQ ID NO:11); and RVVRVVRRWVRRVRRVWRRVVRVVRRWVRRVRRVWRRVVRVVRRWRVV (SEQ ID NO:12).

64. The method of claim 63 wherein the subject is human.

65. The method of claim 64 wherein the cell is a peripheral blood **monocyte**.

L26 ANSWER 48 OF 54 USPATFULL on STN
2002:303714 In situ injection of antigen-presenting cells with genetically enhanced cytokine expression.
Tahara, Hideaki, Tokyo, JAPAN

Lotze, Michael T., Pittsburgh, PA, United States
Nishioka, Yasuhiko, Tokushima, JAPAN
University of Pittsburgh of the Commonwealth System of Higher Education, Pittsburgh, PA, United States (U.S. corporation)
US 6482405 B1 20021119
APPLICATION: US 1999-395836 19990914 (9)
PRIORITY: US 1998-100048P 19980915 (60)
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A method of treating an individual having an tumor comprising: injecting an individual at or near a site of a tumor with an effective amount of genetically modified dendritic cells which have not been pre-**loaded** with tumor associated antigen prior to said injection, wherein said dendritic cells have been genetically modified to enhance expression of IL-12 by transduction with a vector encoding IL-12, whereby the injection of said dendritic cells results in the treatment of said tumor.

2. A method as in claim 1 wherein said dendritic cells have been genetically modified by transduction with a viral vector encoding IL-12.

3. A method as in claim 2 wherein said viral vector is a retroviral vector.

4. A method as in claim 2 wherein said viral vector is selected from the group consisting of adenoviral vectors and adeno-associated viral vectors.

5. A method as in claim 3 wherein said dendritic cells have been genetically modified by centrifuging said dendritic cells with the supernatant of producer cells expressing said retroviral vector encoding IL-12.

6. A method as in claim 1 wherein said dendritic cells are selected from the group consisting of CD34+-derived dendritic cells, bone marrow-derived dendritic cells, **monocyte**-derived dendritic cells, splenocyte derived dendritic cells, skin-derived dendritic cells, follicular dendritic cells, and germinal center dendritic cells.

7. A method as in claim 1 wherein said dendritic cells are CD34+-derived dendritic cells cultured in the presence of at least one factor selected from the group consisting of G-CSF, GM-CSF, TNF-α, IL-4, the Flt-3 ligand and the kit ligand.

8. A method as in claim 1, wherein said dendritic cells are transduced ex vivo.

9. A method as in claim 1, wherein the expression of IL-12 by said dendritic cells results in the reduction in tumor growth.

10. A method as in claim 1, wherein the expression of IL-12 by said dendritic cells results in the delay of tumor growth.

L26 ANSWER 49 OF 54 USPATFULL on STN
2002:297455 Methods and compositions for making dendritic cells from expanded populations of monocytes and for activating T cells.
Nelson, Edward L., Eldersburg, MD, United States
Strobl, Susan L, Hagerstown, MD, United States
The United States of America as represented by the Secretary of the Department of Health and Human Services, Washington, DC, United States

(U.S. government)
US 6479286 B1 20021112
WO 9853048 19991126
APPLICATION: US 2000-424173 20000605 (9)
WO 1999-US9810311 19990520 20000605 PCT 371 date
PRIORITY: US 1997-47348P 19970521 (60)
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A method of expanding a population of **monocytes** from peripheral blood and differentiating the expanded population into dendritic cells, comprising: first incubating the **monocytes** in the presence of IL-3 and under conditions which do not differentiate the **monocytes** into dendritic cells; thereby expanding the population of the **monocytes**; and subsequently incubating the expanded population with GM-CSF and IL-4, thereby differentiating the expanded population of **monocytes** into dendritic cells.

2. The method of claim 1, wherein the IL-3 is present at a concentration of between 5 and about 50 ng/ml.

3. The method of claim 1, further comprising incubating the dendritic cells with TNF-α, thereby generating activated dendritic cells.

4. The method of claim 1, further comprising incubating the dendritic cells with TNF-α, thereby transiently activating the dendritic cells to a proinflammatory state.

5. The method of claim 1, further comprising leukapheresis of peripheral blood mononuclear cells from a patient, thereby providing isolated peripheral blood, followed by elutriation of the isolated peripheral olood to provide isolated **monocytes**, which isolated **monocytes** are incubated in the presence of IL-3.

6. The method of claim 1, further comprising isolating **monocytes** from a patient, which isolated **monocytes** are incubated in the presence of IL-3 to provide said expanded population of **monocytes**.

7. The method of claim 1, further comprising isolating **monocytes** from a patient, which isolated **monocytes** are incubated in the presence of IL-3 to provide said expanded population of **monocytes**, the method further comprising presenting a peptide on the surface of the dendritic cells.

8. The method of claim 1, further comprising isolating **monocytes** from a patient, which isolated **monocytes** are incubated in the presence of IL-3 to provide said expanded population of **monocytes**, further comprising: presenting a peptide on the surface of the dendritic cells, thereby providing a population of antigen presenting dendritic cells; and, activating a population of T cells with the population of antigen presenting dendritic cells, thereby providing an activated population of T cells.

9. The method of claim 8, wherein the step of activating the population of T cells occurs in vitro.

10. The method of claim 8, further comprising exposing the antigen presenting dendritic cells to TNF-α.

11. The method of claim 8, wherein the step of activating the population of T cells occurs in vivo.

12. The method of claim 8, the method further comprising introducing said activated T cells into the patient.

13. The method of claim 8, the method further comprising introducing said antigen presenting dendritic cells into said patient.

14. The method of claim 13, wherein the dendritic cells stimulate NK cell activity in the patient.

15. The method of claim 8, wherein the antigen is derived from a protein or carbohydrate expressed on the surface of a transformed cell.

16. The method of claim 8, wherein the peptide is derived from a protein selected from the group consisting of HIV Gag, HIV Env, c-erb-β-2/HER2/neu, PEM/MUC-1, Int-2, Hst, BRCA-1, BRCA-2, truncated EGFRvIII, MUC-1, p53, ras, RK, Myc, Myb, OB-1, OB-2, BCR/ABL, GIP, GSP, RET, ROS, FIS, SRC, TRC, WTI, DCC, NF1, FAP, MEN-1, ERB-B1 MART-1, gp-100, PSA, HBVc, HBVs, HPV E6, HPV E7, an idiotypic immunoglobulin, tyrosinase, MAGE-1, trp-1, and a mycobacterial antigen.

17. The method of claim 8, wherein the peptide has a carbohydrate epitope.

18. The method of claim 1, further comprising contacting said dendritic cell with a protein differentially expressed on a cell selected from the group consisting of: a cancer cell, a bacterial cell, a parasitically infected cell and a virally infected cell.

19. The method of claim 18, wherein the protein is expressed on the surface of a transformed cell.

20. The method of claim 18, wherein the differentially expressed protein is selected from the group consisting of HIV Gag, HIV Env, HER-2, MART-1, gp-100, PSA, HBVc, HBVs, tyrosinase, MAGE-1, trp-1, mycobacterial antigens, and CEA.

21. The method of claim 1, further comprising transducing said dendritic cell with a nucleic acid vector which encodes a protein differentially expressed on a cell selected from the group consisting of: a cancer cell, a bacterial cell, a parasitically infected cell and a virally infected cell.

22. A method of activating a T cell, comprising: expanding a population of **monocytes** from peripheral blood and differentiating the expanded population into dendritic cells according to the method of claim 1; and, contacting the T cell with at least one of said dendritic cells; thereby producing an activated T-cell.

23. The method of claim 22, wherein the dendritic cell contacts the T cell in vitro.

24. The method of claim 22, wherein the T cell is a helper T cell.

25. The method of claim 22, wherein the dendritic cell presents an antigenic protein comprising a peptide subsequence derived from a peptide expressed on the surface of a cancer cell.

26. The method of claim 25, wherein the activated T cell is competent to kill the cancer cell.

27. The method of claim 25, wherein the activated T cell mediates a helper T cell response.

28. The method of claim 25, wherein the antigen is derived from a protein or carbohydrate expressed on the surface of a transformed cell.

29. The method of claim 25, wherein the activated T cell recognizes an antigen derived from a protein selected from the group consisting of HIV-1 Gag, HIV-1 Env, HER-2, MART-1, gp-100, PSA, HBVc, HBVs, tyrosinase, MAGE-1, trp-1, a mycobacterial antigen, and CEA.

30. A method for detecting the ability of an antigenic protein or peptide to induce T cell mediated anti-cancer cell activity, comprising: expanding a population of **monocytes** from peripheral blood and differentiating the expanded population into dendritic cells according to the method of claim 1; loading the antigenic protein or peptide onto the dendritic cells; contacting a T-cell with at least one of the **loaded** dendritic cells, thereby providing an activated T cell; contacting a cancer cell with the activated T cell; and, monitoring the effect of the activated T cell on the cancer cell; thereby detecting the anti-cancer cell activity of the T cell activated by contact with the dendritic cell comprising the antigenic protein or peptide.

31. The method of claim 30, wherein the antigenic peptide is derived from HER-2, and the cancer cell is a breast cancer cell.

32. The method of claim 30, wherein the antigenic peptide is derived from a protein selected from the group consisting of MART-1 and gp-100, wherein the cancer cell is a melanoma cell.

33. The method of claim 30, wherein the antigenic peptide is derived from CEA and the cancer cell is a colon cancer cell.

34. The method of claim 30, wherein the T cell is contacted with the dendritic cell in vivo.

35. The method of claim 30, wherein the T cell is contacted with the dendritic cell in vitro.

36. The method of claim 30, wherein the T cell is contacted with the dendritic cell in vitro and contacted with the cancer cell in vitro.

37. The method of claim 30, wherein the T cell is contacted with the dendritic cell in vivo and contacted with the cancer cell in vivo.

38. A method of killing a target cell, comprising: expanding a population of **monocytes** from peripheral blood and differentiating the expanded population into dendritic cells according to the method of claim 1; loading the dendritic cells with an antigenic protein or peptide fragment of the target cell; contacting the T-cell with at least one of the **loaded** dendritic cells to activate the T-cell by; and contacting the target cell with the activated T cell.

39. The method of claim 38, wherein the target cell is contacted by the activated T cell in vivo.

40. The method of claim 38, wherein the target cell is contacted by the activated T cell in vitro.

41. The method of claim 38, wherein the target cell is selected from the group consisting of a cancer cell, an intracellularly infected with a bacterial cell, and, a virally-infected cell.

42. A method of making a pharmaceutical composition comprising a

pharmaceutically acceptable carrier and a population of at least about 106 antigen-**loaded** dendritic cells; said method comprising: expanding a population of **monocytes** from peripheral blood and differentiating the expanded population into dendritic cells according to the method of claim 1; and loading a heterologous protein or peptide onto the dendritic cells to make the antigen-**loaded** dendritic cells; wherein the **loaded** dendritic cells are competent to activate T-cells to kill a target cell in vitro; and formulating the antigen **loaded** dendritic cells in a pharmaceutically acceptable carrier.

43. The method of claim 42, wherein the dendritic cells are made from an expanded population of **monocytes** by incubating the population with IL-4 and GM-CSF and with one or more additional ligands selected from IL-1α, IL-1β and Cd40 ligand.

44. The method of claim 42, wherein the dendritic cells are primarily activated dendritic cells.

45. The method of claim 42, wherein the population of dendritic cells is competent to activate said T cells against said target cell in vivo.

46. The method of claim 42, wherein the heterologous protein is selected from the group of proteins consisting of HER-2, MART-1, gp-100, PSA, HBVc, HBVs, tyrosinase, MAGE-1, trp-1 and CEA.

47. The method of claim 42, wherein formulating the antigen **loaded** dendritic cells in a pharmaceutically acceptable carrier further comprises formulating the antigen **loaded** dendritic cells with a T cell in a pharmaceutically acceptable carrier.

48. The method of claim 42, wherein the target cell is a cancer cell.

49. The method of claim 1, wherein said **monocytes** are CD14+ **monocytes**.

50. The method of claim 30, wherein said **monocytes** are CD14+ **monocytes**.

51. The method of claim 30, wherein said **monocytes** are CD14+ **monocytes**.

52. The method of claim 38, wherein said **monocytes** are CD14+ **monocytes**.

53. The method of claim 42, wherein said **monocytes** are CD14+ **monocytes**.

L26 ANSWER 50 OF 54 USPATFULL on STN
2002:31949 Methods for treating cancers and pathogen infections using antigen-presenting cells loaded with RNA.
Nair, Smita K., Durham, NC, UNITED STATES
Boczkowski, David J., Durham, NC, UNITED STATES
Gilboa, Eli, Durham, NC, UNITED STATES
US 2002018769 A1 20020214
APPLICATION: US 2001-875264 A1 20010607 (9)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A method for producing an RNA-**loaded** antigen presenting cell (APC), said method comprising: introducing into an antigen-presenting cell in vitro RNA selected from the group consisting of (i) tumor-derived RNA

comprising tumor-specific RNA and (ii) pathogen-derived RNA comprising pathogen-specific RNA, thereby producing an RNA-**loaded** APC.

2. The method of claim 1, wherein said APC is a dendritic cell.

3. The method of claim 1, wherein said APC is a **macrophage**.

4. The method of claim 1, wherein said APC is an endothelial cell.

5. The method of claim 1, wherein said APC is an artificially generated APC.

6. The method of claim 1, wherein said RNA is tumor-derived RNA that comprises poly A+ RNA.

7. The method of claim 1, wherein said RNA is tumor-derived RNA that comprises cytoplasmic RNA.

8. The method of claim 1, wherein said RNA corresponds to a tumor antigen.

9. The method of claim 1, wherein said RNA corresponds to a pathogen antigen.

10. The method of claim 1, wherein said RNA corresponds to an epitope.

11. The method of claim 1, wherein said RNA is tumor-specific RNA.

12. The method of claim 1, wherein the RNA is introduced into the APC by contacting the APC with the RNA in the presence of a cationic lipid.

13. The method of claim 1, wherein said RNA is tumor-derived RNA that is provided as a fractionated tumor extract that is fractionated with respect to a non-RNA component of the tumor.

14. An RNA-**loaded** APC produced by the method of claim 1.

15. A method for treating or preventing tumor formation in a patient, said method comprising administering to the patient a therapeutically effective amount of the RNA-**loaded** APC of claim 14, wherein tumor-derived RNA is introduced into said APC.

16. The method of claim 15, wherein the tumor-derived RNA is derived from said patient.

17. The method of claim 15, wherein the tumor-derived RNA is derived from a donor patient.

18. A method for treating or preventing a pathogen infection in a patient, said method comprising administering to the patient a therapeutically effective amount of the RNA-**loaded** APC of claim 14, wherein pathogen-derived RNA is introduced into said APC.

19. A method for producing a cytotoxic T lymphocyte (CTL), said method comprising: providing a T lymphocyte; contacting said T lymphocyte in vitro with the RNA-**loaded** APC of claim 14; and maintaining said T lymphocyte under conditions conducive to CTL proliferation, thereby producing a CTL.

20. A CTL produced by according to the method of claim 19.

21. A method for treating or preventing tumor formation in a patient,

said method comprising administering to the patient a therapeutically effective amount of the CTL of claim 20, wherein said APC is **loaded** with tumor-derived RNA.

22. The method of claim 21, wherein the T lymphocyte is derived from said patient.

23. The method of claim 21, wherein the T lymphocyte is derived from a donor patient.

24. The method of claim 21, wherein the tumor-derived RNA is derived from a tumor of said patient.

25. The method of claim 21, wherein the tumor-derived RNA is derived from a donor patient.

26. A method for treating or preventing pathogen infection in a patient, said method comprising administering to the patient a therapeutically effective amount of the CTL of claim 15, wherein said APC is **loaded** with pathogen-derived RNA.

27. The method of claim 1, wherein the tumor-derived RNA is derived from a melanoma.

28. The method of claim 1, wherein the tumor-derived RNA is derived from a bladder tumor.

29. The method of claim 1, wherein the tumor-derived RNA is derived from a tumor selected from the group consisting of breast cancer tumors, colon cancer tumors, prostate cancer tumors, and ovarian cancer tumors.

30. The method of claim 1, wherein said pathogen-derived RNA is derived from a virus.

31. The method of claim 30, wherein said virus is selected from the group consisting of Hepatitis viruses, human immunodeficiency viruses, influenza viruses, poliomyelitis viruses, measles viruses, herpes viruses, mumps viruses, and rubella viruses.

32. The method of claim 1, wherein said pathogen-derived RNA is derived from a bacterium.

33. The method of claim 32, wherein said bacterium is selected from the group consisting of Salmonella, Shigella, and Enterobacter.

34. The method of claim 1, wherein said pathogen-derived RNA is derived from an intracellular pathogen.

35. The method of claim 1, wherein said RNA is isolated from a cell.

36. The method of claim 1, wherein said RNA is prepared by PCR amplification and in vitro transcription.

37. The method of claim 1, wherein said RNA is tumor-derived RNA that comprises nuclear RNA.

38. The method of claim 1 wherein said RNA corresponds to a minigene.

L26 ANSWER 51 OF 54 USPATFULL on STN
2002:26892 Proteins deposited onto sparingly soluble biocompatible particles for controlled protein release into a biological environment from a polymer

matrix.
Shih, Chung, Sandy, UT, UNITED STATES
Zentner, Gaylen, Salt Lake City, UT, UNITED STATES
Piao, Ai-Zhi, Salt Lake City, UT, UNITED STATES
MacroMed, Incorporated (U.S. corporation)
US 2002015737 A1 20020207
APPLICATION: US 2001-827100 A1 20010405 (9)
PRIORITY: US 2000-195700P 20000407 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A drug delivery system for controlled protein release into a biological environment comprising: a) a sparingly soluble biocompatible particle; b) an effective amount of a protein or peptide deposited onto the particle forming a substantially insoluble protein-particle combination; and c) a biocompatible polymeric matrix having dispersed therein the protein-particle combination.

2. The drug delivery system of claim 1 wherein the protein-particle combination has a biocompatible particle to protein or peptide ratio from about 1:10 to 100,000:1 by weight.

3. The drug delivery system of claim 1 wherein the protein-particle combination has a biocompatible particle to protein or peptide ratio from about 1:10 to 1000:1 by weight.

4. The drug delivery system of claim 1 wherein the protein-particle combination is present in relation to polymeric matrix at from about 0.01 to 30% by weight.

5. The drug delivery system of claim 1 wherein said biocompatible particle is a sparingly soluble salt or oxide selected from the group consisting of zinc salts, zinc oxides, magnesium salts, magnesium oxides, calcium salts, and calcium oxides.

6. The drug delivery system of claim 1 wherein said biocompatible particle is selected from the group consisting of zinc carbonate, zinc oxide, zinc tartrate, zinc hydroxide, zinc phosphate, zinc citrate, magnesium oxide, magnesium hydroxide, magnesium carbonate, calcium oxide, calcium phosphate, calcium sulfate, calcium carbonate, and combinations thereof.

7. The drug delivery system of claim 1 wherein said protein or peptide is selected from the group consisting of oxytocin, vasopressin, adrenocorticotropic hormone, epidermal growth factor, platelet-derived growth factor (PDGF), prolactin, luteinizing hormone releasing hormone (LHRH), LHRH agonists, LHRH agonists, growth hormone, growth hormone releasing factor, insulin, erythropoietin, somatostatin, glucagon, interleukin (including IL-2, IL-11, IL-12, etc.), interferon-α, interferon-β, interferon-γ, gastrin, tetragastrin, pentagastrin, urogastrone, secretin, calcitonin, enkephalins, endorphins, angiotensins, thyrotropin releasing hormone (TRH), tumor necrosis factor (TNF), parathyroid hormone (PTH), nerve growth factor (NGF), granulocyte-colony stimulating factor (G-CSF), granulocyte **macrophage**-colony stimulating factor (GM-CSF), **macrophage**-colony stimulating factor (M-CSF), heparinase, vascular endothelial growth factor (VEG-F), bone morphogenic protein (BMP), hANP, glucagon-like peptide (GLP-1), renin, bradykinin, bacitracins, polymyxins, colistins, tyrocidine, gramicidins, cyclosporins, enzymes, cytokines, antibodies, vaccines, antibiotics, antibodies, glycoproteins, and combinations thereof.

8. The drug delivery system of claim 1 wherein said protein is selected from the group consisting of human growth hormone and insulin.

9. The drug delivery system of claim 1 wherein said biocompatible polymeric matrix is selected from the group consisting of polymeric particles, implants, microcapsules, microspheres, nanospheres, polymeric gels, environment responsive polymers or gels, and combinations thereof.

10. The drug delivery system of claim 1 wherein said biocompatible polymeric matrix is comprised of a polymer or gel material selected from the group consisting of nondegradable polymers, biodegradable polymers, absorbable polymers, bioerodible polymers, block copolymers, and combinations thereof.

11. The drug delivery system of claim 10 wherein said biocompatible polymeric matrix is comprised of a biodegradable polymer selected from the group consisting of poly(lactide)s, poly(glycolide)s, poly(lactide-co-glycolide)s, poly(lactic acid)s, poly(glycolic acid)s, poly(lactic acid-co-glycolic acid)s, polyanhydrides, poly(ortho ester)s, poly(ε-caprolactone), poly(hydroxybutyric acid), polyaminoacids, and blends and copolymers thereof.

12. The drug delivery system of claim 10 wherein said biocompatible polymeric matrix is a block copolymer selected from the group consisting of A-B-A block copolymers, B-A-B block copolymers, A-B block copolymers, and combinations thereof, and wherein said A block is a biodegradable polymer selected from the group consisting of poly(lactide)s, poly(glycolide)s, poly(lactide-co-glycolide)s, poly(lactic acid)s, poly(glycolic acid)s, poly(lactic acid-co-glycolic acid)s, polyanhydrides, poly(ε-caprolactone)s, poly(hydroxybutyric acid)s, poly(aminoacids)s, poly(ortho ester)s, and blends and copolymers thereof, and said B block is polyethylene glycol.

13. The drug delivery system of claim 10 wherein said biocompatible polymeric matrix is comprised of a nondegradable polymer selected from the group consisting of polyacrylates, polyacrylate esters, silicone rubbers, poloxamers, tetronics, polyethylenes, poly(methyl methacrylate)s, polymethyl methacrylate esters, polystyrenes, ethylene-vinyl acetate copolymers, polyethylene-maleic anhydride copolymers, polyamides, polymers of ethylene-vinyl acetates, acyl substituted cellulose acetates, nondegradable polyurethanes, poly(vinyl chloride)s, poly(vinyl fluoride)s, poly(vinyl imidazole)s, chlorosulphonate polyolefins, poly(ethylene oxide)s, and blends and copolymers thereof.

14. The drug delivery system of claim 1 wherein the protein or peptide is deposited onto a surface of the particle.

15. The drug delivery system of claim 1 wherein a plurality of protein or peptide molecules are present, a first portion of said plurality of protein or peptide molecules are deposited on the particle and dispersed within the polymeric matrix, and a second portion of said plurality of protein or peptide molecules are dispersed within the polymeric matrix.

16. The drug delivery system of claim 1 further comprising a second protein or peptide.

17. The drug delivery system of claim 16 wherein the second protein or peptide is deposited on the particle dispersed within the polymeric matrix.

18. The drug delivery system of claim 16 wherein the second protein or

peptide is dispersed within the polymeric matrix.

19. The drug delivery system of claim 16 wherein a plurality of second protein or peptide molecules are present, a first portion of said plurality of second protein or peptide molecules are deposited on the particle and dispersed within the polymeric matrix, and a second portion of said plurality of second protein or peptide molecules are dispersed within the polymeric matrix.

20. A method for controlled delivery of a protein to a warm-blooded animal comprising: a) depositing a protein or peptides onto a sparingly soluble biocompatible particle to form a protein-particle combination; b) loading the protein-particle combination in a biocompatible polymeric matrix; and c) administering the **loaded** biocompatible polymeric matrix to a warm-blooded animal.

21. The method of claim 20 wherein the protein-particle combination has a biocompatible particle to protein or peptide ratio from about 1:10 to 100,000:1 by weight.

22. The method of claim 20 wherein the protein-particle combination has a biocompatible particle to protein or peptide ratio from about 1:10 to 1000:1 by weight.

23. The method of claim 20 wherein the protein-particle combination is present in relation to polymeric matrix at from about 0.01 to 30% by weight.

24. The method of claim 20 wherein the **loaded** biocompatible polymeric matrix is delivered by a route selected from the group consisting of parenteral, ocular, topical, implantation, inhalation, vaginal, buccal, transmucosal, transurethral, rectal, nasal, pulmonary, and combinations thereof.

25. The method of claim 24 wherein the route of administration is parenteral.

26. The method of claim 20 wherein said biocompatible particle is a sparingly soluble salt or oxide selected from the group consisting of zinc salts, zinc oxides, magnesium salts, magnesium oxides, calcium salts, and calcium oxides.

27. The method of claim 20 wherein said sparingly soluble particle is selected from the group consisting of zinc carbonate, zinc oxide, zinc tartrate, zinc hydroxide, zinc phosphate, zinc citrate, magnesium oxide, magnesium hydroxide, magnesium carbonate, calcium oxide, calcium phosphate, calcium sulfate, calcium carbonate, and combinations thereof.

28. The method of claim 20 wherein said protein or peptide is selected from the group consisting of oxytocin, vasopressin, adrenocorticotropic hormone, epidermal growth factor, platelet-derived growth factor (PDGF), prolactin, luteinizing hormone releasing hormone (LHRH), LHRH agonists, LHRH agonists, growth hormone, growth hormone releasing factor, insulin, erythropoietin, somatostatin, glucagon, interleukin (including IL-2, IL-11, IL-12, etc.), interferon-α, interferon-β, interferon-γ, gastrin, tetragastrin, pentagastrin, urogastrone, secretin, calcitonin, enkephalins, endorphins, angiotensins, thyrotropin releasing hormone (TRH), tumor necrosis factor (TNF), parathyroid hormone (PTH), nerve growth factor (NGF), granulocyte-colony stimulating factor (G-CSF), granulocyte **macrophage**-colony stimulating factor (GM-CSF), **macrophage**-colony stimulating factor (M-CSF), heparinase, vascular endothelial growth factor (VEG-F), bone morphogenic protein

(BMP), hANP, glucagon-like peptide (GLP-1), renin, bradykinin, bacitracins, polymyxins, colistins, tyrocidine, gramicidins, cyclosporins, enzymes, cytokines, antibodies, vaccines, antibiotics, antibodies, glycoproteins, and combinations thereof.

29. The method of claim 20 wherein said protein is selected from the group consisting of human growth hormone and insulin.

30. The method of claim 20 wherein said biocompatible polymeric matrix is selected from the group consisting of polymeric particles, implants, microcapsules, microspheres, nanospheres, polymeric gels, environment responsive polymers or gels, and combinations thereof.

31. The method of claim 20 wherein said biocompatible polymeric matrix is comprised of a polymer material selected from the group consisting of nondegradable polymers, biodegradable polymers, absorbable polymers, bioerodible polymers, block copolymers, and combinations thereof.

32. The method of claim 31 wherein said biocompatible polymeric matrix is comprised of a biodegradable polymer selected from the group consisting of poly(lactide)s, poly(glycolide)s, poly(lactide-co-glycolide)s, poly(lactic acid)s, poly(glycolic acid)s, poly(lactic acid-co-glycolic acid)s, polyanhydrides, poly(ortho ester)s, poly(ε-caprolactone), poly(hydroxybutyric acid), polyaminoacids, and blends and copolymers thereof.

33. The method of claim 31 wherein said biocompatible polymeric matrix is a block copolymer selected from the group consisting of A-B-A block copolymers, B-A-B block copolymers, A-B block copolymers, and combinations thereof, and wherein said A block is a biodegradable polymer selected from the group consisting of poly(lactide)s, poly(glycolide)s, poly(lactide-co-glycolide)s, poly(lactic acid)s, poly(glycolic acid)s, poly(lactic acid-co-glycolic acid)s, polyanhydrides, polycaprolactones, poly(ε-caprolactone)s, poly(hydroxybutyric acid)s, poly(aminoacids)s, poly(ortho ester)s, and blends and copolymers thereof, and said B block is polyethylene glycol.

34. The method of claim 31 wherein said biocompatible polymeric matrix is comprised of a nondegradable polymer selected from the group consisting of polyacrylates, polyacrylate esters, silicone rubbers, poloxamers, tetronics, polyethylenes, poly(methyl methacrylate)s, polymethyl methacrylate esters, polystyrenes, ethylene-vinyl acetate copolymers, polyethylene-maleic anhydride copolymers, polyamides, polymers of ethylene-vinyl acetates, acyl substituted cellulose acetates, nondegradable polyurethanes, poly(vinyl chloride)s, poly(vinyl fluoride)s, poly(vinyl imidazole)s, chlorosulphonate polyolefins, poly(ethylene oxide)s, and blends and copolymers thereof.

35. The method of claim 20 wherein a plurality of protein or peptide molecules are present, a first portion of said plurality of protein or peptide molecules are deposited on the particle and dispersed within the polymeric matrix, and a second portion of said plurality of protein or peptide molecules are dispersed within the polymeric matrix.

36. The method of claim 20 further comprising a second protein or peptide.

37. The method of claim 36 wherein the second protein or peptide is deposited on the particle dispersed within the polymeric matrix.

38. The method of claim 36 wherein the second protein or peptide is dispersed within the polymeric matrix.

39. The method of claim 36 wherein a plurality of second protein or peptide molecules are present, a first portion of said plurality of second protein or peptide molecules are deposited on the particle and dispersed within the polymeric matrix, and a second portion of said plurality of second protein or peptide molecules are dispersed within the polymeric matrix.

40. A method of preparing a protein delivery system comprising: a) depositing a protein or peptide onto a sparingly soluble biocompatible particle to form a protein-particle combination; and b) loading the protein-particle combination in a biocompatible polymeric matrix.

41. The method of claim 40 wherein the protein-particle combination has a biocompatible particle to protein or peptide ratio from about 1:10 to 100,000:1 by weight.

42. The method of claim 40 wherein the protein-particle combination has a biocompatible particle to protein or peptide ratio from about 1:10 to 1000:1 by weight.

43. The method of claim 40 wherein the protein-particle combination is present in relation to polymeric matrix at from about 0.01 to 30% by weight.

44. The method of claim 40 wherein the protein or peptide is deposited onto the particle by a mechanism selected from the group consisting of adsorption, absorption, and coprecipitation.

45. The method of claim 40 wherein the protein or peptide is deposited onto a surface of the particle.

46. The method of claim 40 wherein said biocompatible particle is a sparingly soluble salt or oxide selected from the group consisting of zinc salts, zinc oxides, magnesium salts, magnesium oxides, calcium salts, and calcium oxides.

47. The method of claim 40 wherein said sparingly soluble particle is selected from the group consisting of zinc carbonate, zinc oxide, zinc tartrate, zinc hydroxide, zinc phosphate, zinc citrate, magnesium oxide, magnesium hydroxide, magnesium carbonate, calcium oxide, calcium phosphate, calcium sulfate, calcium carbonate, and combinations thereof.

48. The method of claim 30 wherein said protein or peptide is selected from the group consisting of oxytocin, vasopressin, adrenocorticotropic hormone, epidermal growth factor, platelet-derived growth factor (PDGF), prolactin, luteinizing hormone releasing hormone (LHRH), LHRH agonists, LHRH agonists, growth hormone, growth hormone releasing factor, insulin, erythropoietin, somatostatin, glucagon, interleukin (including IL-2, IL-11, IL-12, etc.), interferon-α, interferon-β, interferon-γ, gastrin, tetragastrin, pentagastrin, urogastrone, secretin, calcitonin, enkephalins, endorphins, angiotensins, thyrotropin releasing hormone (TRH), tumor necrosis factor (TNF), parathyroid hormone (PTH), nerve growth factor (NGF), granulocyte-colony stimulating factor (G-CSF), granulocyte **macrophage**-colony stimulating factor (GM-CSF), **macrophage**-colony stimulating factor (M-CSF), heparinase, vascular endothelial growth factor (VEG-F), bone morphogenic protein (BMP), hANP, glucagon-like peptide (GLP-1), renin, bradykinin, bacitracins, polymyxins, colistins, tyrocidine, gramicidins, cyclosporins, enzymes, cytokines, antibodies, vaccines, antibiotics, antibodies, glycoproteins, and combinations thereof.

49. The method of claim 40 wherein said protein is selected from the group consisting of human growth hormone and insulin.

50. The method of claim 40 wherein said biocompatible polymeric matrix is selected from the group consisting of polymeric particles, implants, microcapsules, microspheres, nanospheres, polymeric gels, environment responsive polymers or gels, and combinations thereof.

51. The method of claim 40 wherein said biocompatible polymeric matrix is comprised of a polymer material selected from the group consisting of nondegradable polymers, biodegradable polymers, absorbable polymers, bioerodible polymers, block copolymers, and combinations thereof.

52. The method of claim 51 wherein said biocompatible polymeric matrix is comprised of a biodegradable polymer selected from the group consisting of poly(lactide)s, poly(glycolide)s, poly(lactide-co-glycolide)s, poly(lactic acid)s, poly(glycolic acid)s, poly(lactic acid-co-glycolic acid) s, polyanhydrides, poly(ortho ester) s, poly(ε-caprolactone), poly(hydroxybutyric acid), polyaminoacids, and blends and copolymers thereof.

53. The method of claim 51 wherein said biocompatible polymeric matrix is a block copolymer selected from the group consisting of A-B-A block copolymers, B-A-B block copolymers, A-B block copolymers, and combinations thereof, and wherein said A block is a biodegradable polymer selected from the group consisting of poly(lactide)s, poly(glycolide)s, poly(lactide-co-glycolide)s, poly(lactic acid)s, poly(glycolic acid)s, poly(lactic acid-co-glycolic acid)s, polyanhydrides, poly(ε-caprolactone)s, poly(hydroxybutyric acid)s, poly(aminoacids)s, poly(ortho ester)s, and blends and copolymers thereof, and said B block is polyethylene glycol.

54. The method of claim 51 wherein said biocompatible polymeric matrix is comprised of a nondegradable polymer selected from the group consisting of polyacrylates, polyacrylate esters, silicone rubbers, poloxamers, tetronics, polyethylenes, poly(methyl methacrylate)s, polymethyl methacrylate esters, polystyrenes, ethylene-vinyl acetate copolymers, polyethylene-maleic anhydride copolymers, polyamides, polymers of ethylene-vinyl acetates, acyl substituted cellulose acetates, nondegradable polyurethanes, poly(vinyl chloride)s, poly(vinyl fluoride)s, poly(vinyl imidazole)s, chlorosulphonate polyolefins, poly(ethylene oxide)s, and blends and copolymers thereof.

55. A drug delivery system for controlled protein release into a biological environment comprising: a) a sparingly soluble biocompatible particle selected from the group consisting of zinc salts, zinc oxides, magnesium salts, magnesium oxides, calcium salts, calcium oxides, and combinations thereof; b) an effective amount of a protein or peptide deposited onto the particle forming a substantially insoluble protein-particle combination, wherein the protein-particle combination has a biocompatible particle to protein or peptide ratio from about 1:10 to 100,000:1 by weight; and c) a biocompatible polymeric matrix having dispersed therein the protein-particle combination, wherein the protein-particle combination is present in relation to polymeric matrix at from about 0.01 to 30% by weight.

56. A drug delivery system for controlled protein release into a biological environment comprising: a) a sparingly soluble biocompatible particle; b) an effective amount of a protein or peptide deposited onto the particle forming a substantially insoluble protein-particle combination; and c) a biocompatible polymeric matrix said comprised of a polymer or gel material selected from the group consisting of

nondegradable polymers, biodegradable polymers, absorbable polymers, bioerodible polymers, block copolymers, and combinations thereof, said polymeric matrix in a form selected from the group consisting of polymeric particles, implants, microcapsules, microspheres, nanospheres, polymeric gels, environment responsive polymers or gels, and combinations thereof, said polymeric matrix having dispersed therein the protein-particle combination.

L26 ANSWER 52 OF 54 USPATFULL on STN
2001:184835 Methods for treating cancers and pathogen infections using antigen-presenting cells loaded with RNA.
Nair, Smita K., Durham, NC, United States
Boczkowski, David J., Durham, NC, United States
Gilboa, Eli, Durham, NC, United States
Duke University, Durham, NC, United States (U.S. corporation)
US 6306388 B1 20011023
APPLICATION: US 1998-73819 19980506 (9)
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A method for producing an RNA-**loaded** antigen presenting cell (APC), said method comprising: introducing into an antigen-presenting cell in vitro RNA selected from the group consisting of (i) RNA comprising tumor-specific RNA and (ii) RNA comprising pathogen-specific RNA, thereby producing an RNA-**loaded** APC.

2. The method of claim 1, wherein said APC is a dendritic cell.

3. The method of claim 1, wherein said APC is a **macrophage**.

4. The method of claim 1, wherein said APC is an endothelial cell.

5. The method of claim 1, wherein said APC is an artificially generated APC.

6. The method of claim 1, wherein said RNA comprises tumor specific RNA that comprises poly A+ RNA.

7. The method of claim 1, wherein said RNA comprises tumor-specific RNA that comprises cytoplasmic RNA.

8. The method of claim 1, wherein said RNA corresponds to a tumor antigen.

9. The method of claim 1, wherein said RNA corresponds to a pathogen antigen.

10. The method of claim 1, wherein said RNA corresponds to an epitope.

11. The method of claim 1, wherein said RNA is tumor-specific RNA.

12. The method of claim 1, wherein the RNA is introduced into the APC by contacting the APC with the RNA in the presence of a cationic lipid.

13. The method of claim 1, wherein said RNA comprises tumor-specific RNA that is provided as a tumor extract that is fractionated with respect to a non-RNA component of the tumor.

14. An RNA-**loaded** APC produced by the method of claim 1.

15. The method of claim 1, wherein the tumor-specific RNA comprises

melanoma-specific RNA.

16. The method of claim 1, wherein the tumor-specific RNA comprises bladder tumor-specific RNA.

17. The method of claim 1, wherein the tumor-specific RNA comprises tumor-specific RNA selected from the group consisting of breast cancer-specific RNA, colon cancer-specific RNA, prostate cancer-specific RNA and ovarian cancer-specific RNA.

18. The method of claim 1, wherein said pathogen-specific RNA comprises viral RNA.

19. The method of claim 18, wherein said virus is selected from the group consisting of Hepatitis viruses, human immunodeficiency viruses, influenza viruses, poliomyelitis viruses, measles viruses, herpes viruses, mumps viruses, and rubella viruses.

20. The method of claim 1, wherein said pathogen-specific RNA comprises bacterial RNA.

21. The method of claim 20, wherein said bacterium is selected from the group consisting of Salmonella, Shigella, and Enterobacter.

22. The method of claim 1, wherein said RNA is isolated from a cell.

23. The method of claim 1, wherein said RNA is prepared by PCR amplification and in vitro transcription.

24. The method of claim 1, wherein said RNA is tumor-specific RNA that comprises nuclear RNA.

25. The method of claim 1 wherein said RNA corresponds to a minigene.

26. The method according to claim 1 wherein said RNA consists of tumor-specific RNA encoding a specific antigen.

27. The method according to claim 1 wherein said RNA consists of pathogen-specific RNA encoding a specific pathogen antigen.

28. The method according to claim 1 wherein said APC is a professional APC.

29. The method according to claim 1 wherein said RNA is transcribed from cloned cDNA.

L26 ANSWER 53 OF 54 USPATFULL on STN
2001:152505 Agent delivering system comprised of microparticle and biodegradable gel with an improved releasing profile and methods of use thereof.
Shih, Chung, Sandy, UT, United States
Zentner, Gaylen M., Salt Lake City, UT, United States
MacroMed, Inc., Sandy, UT, United States (U.S. corporation)
US 6287588 B1 20010911
APPLICATION: US 2000-559507 20000427 (9)
PRIORITY: US 1999-131562P 19990429 (60)
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A dual phase polymeric agent-delivery composition comprising: (a) a continuous biocompatible gel phase, (b) a discontinuous particulate

phase comprising defined microparticles; and (c) an agent to be delivered contained in both the continuous biocompatible gel phase and the discontinuous particulate phase.

2. The composition according to claim 1 wherein the biocompatible gel phase is biodegradable.

3. The composition according to claim 2 wherein said biodegradable gel comprises a hydrogel.

4. The composition according to claim 3 wherein said hydrogel is a stimuli responsive gel.

5. The composition according to claim 4 wherein said stimuli responsive gel is sensitive to stimuli selected from the group consisting of temperature, pH, ionic strength, solvent, pressure, stress, light intensity, electric field, magnetic field and gelating agents.

6. The composition according to claim 5 wherein said continuous gel phase is formed from block copolymers comprising an effective amount of biodegradable hydrophobic polyester A polymer blocks and polyethylene glycol B polymer blocks.

7. The composition according to claim 6 wherein the effective amount of biodegradable hydrophobic polyester A polymer blocks is 10-83% by weight of said block copolymer.

8. The composition according to claim 5 wherein said continuous gel phase is formed from a reverse thermal gelation (RTG) system comprising an effective amount of block copolymers comprising biodegradable hydrophobic polyester A polymer blocks and polyethylene glycol B polymer blocks.

9. The composition according to claim 8 wherein said RTG system is a mixture of two or more said block copolymers having different gelation properties.

10. The composition according to claim 9 wherein said RTG system comprises tri-block copolymers.

11. The composition according to claim 10 wherein said tri-block polymer comprises about 51 to 83% by weight of said biodegradable hydrophobic polyester, and about 17 to 49% by weight of polyethylene glycol(PEG).

12. The composition according to claim 8 wherein the biodegradable hydrophobic polyester is synthesized from monomers selected from the group consisting of D,L-lactide, D-lactide, L-lactide, D,L-lactic acid, D-lactic acid, L-lactic acid, glycolide, glycolic acid, ε-caprolactone, ε-hydroxy hexanoic acid, and copolymers thereof.

13. The composition according to claim 12 wherein the biodegradable hydrophobic polyester is synthesized from monomers selected from the group consisting of D,L-lactide, D-lactide, L-lactide, D,L-lactic acid, D-lactic acid, L-lactic acid, glycolide, glycolic acid, and copolymers thereof.

14. The composition according to claim 8 wherein the biodegradable hydrophobic polyester comprises between about 20 to 100 mole percent lactide and between about 0 to 80 mole percent glycolide.

15. The composition according to claim 10 wherein, in the triblock

copolymer, each biodegradable block has an average molecular weight of between about 270 and 3000.

16. The composition according to claim 1 wherein said microparticle is in the form of a member selected from the group consisting of microcapsules, microspheres, and nanospheres.

17. The composition according to claim 16 wherein said microparticle is in the form of a member selected from the group consisting of microcapsules and microspheres.

18. The composition according to claim 1 wherein said microparticle is biodegradable.

19. The composition according to claim 18 wherein said agent is a bioactive agent, a drug, or any agent which can be **loaded** to the microparticle.

20. The composition according to claim 19 wherein said drug is a polypeptide or protein, oligonucleotide or gene, hormone, anti-cancer or anti-cell proliferation agent.

21. The composition according to claim 20 wherein said drug is a polypeptide or protein and is a member selected from the group consisting of oxytocin, vasopressin, adrenocorticotropic hormone, epidermal growth factor, platelet-derived growth factor (PDGF), prolactin, luliberin, luteinizing hormone releasing hormone (LHRH), LHRH agonists, LHRH antagonists, growth hormone (human, porcine, bovine, etc.), growth hormone releasing factor, insulin, erythropoietin, somatostatin, glucagon, interleukin-2 (IL-2), interferon-α, β, or γ, gastrin, tetragastrin, pentagastrin, urogastrone, secretin, calcitonin, enkephalins, endorphins, angiotensins, thyrotropin releasing hormone (TRH), tumor necrosis factor (TNF), nerve growth factor (NGF), granulocyte-colony stimulating factor (G-CSF), granulocyte **macrophage**-colony stimulating factor (GM-CSF), **macrophage**-colony stimulating factor (M-CSF), heparinase, bone morphogenic protein (BMP), HANP, glucagon-like peptide (GLP-1), interleukin-11 (IL-11), interleukin-12 (IL-12), VEG-F, recombinant hepatitis B surface antigen (rHBsAg), renin, bradykinin, bacitracins, polymyxins, colistins, tyrocidine, gramicidins, cyclosporins and synthetic analogues, modifications and pharmacologically active fragments thereof, enzymes, cytokines, antibodies and vaccines.

22. The composition according to claim 1 wherein the microparticle content of said composition is between about 0.0001 and 30% by weight.

23. The composition according to claim 1 wherein the drug content of said microparticle is between about 0.001 and 30% by weight.

24. The composition according to claim 21 wherein said polypeptide or protein is a member selected from the group consisting of erythropoietin, luteinizing hormone releasing hormone (LHRH), LHRH agonists, LHRH antagonists, growth hormones (human, porcine, bovine, etc.), tumor necrosis factor (TNF), nerve growth factor (NGF), granulocyte-colony stimulating factor (G-CSF), granulocyte **macrophage**-colony stimulating factor (GM-CSF), **macrophage**-colony stimulating factor (M-CSF), glucagon-like peptide (GLP-1), interleukin-11 (IL-11), interleukin-12 (IL-12), VEG-F, recombinant hepatitis B surface antigen(rHBsAg), cyclosporins and synthetic analogues, modifications and pharmacologically active fragments thereof.

25. The composition according to claim 24 wherein said polypetide or

protein is a human growth hormone, or synthetic analogue, modification and pharmacologically active fragment thereof.

26. The composition according to claim 19 wherein said drug is a member selected from the group consisting of testosterone, estradiol, progesterone, prostaglandins, leuprolide acetate, and synthetic analogues, modifications and pharmaceutically equivalents thereof.

27. The composition according to claim 19 wherein said drug is an anti-cancer agent selected from the group consisting of mitomycin, bleomycin, BCNU, carboplatin, doxorubicin, daunorubicin, methotrexate, paclitaxel, taxotere, actinomycin D, camptothecin, and synthetic analogues, modifications and pharmaceutically equivalents thereof.

28. The composition according to claim 1 further comprising a second agent.

29. The composition according to claim 28 wherein the second agent is a bioactive agent or a drug.

30. The composition according to claim 29 wherein some microparticles contain the first agent and other microparticles contain the second agent.

31. The composition according to claim 29 wherein the gel matrix contains both the first and the second agent.

32. The composition according to claim 28 wherein the second agent is an agent regulating the release profile of the microparticle.

33. A method for delivering an agent to a biological environment in a controlled manner for a prolonged period of time, comprising the steps of: (1) providing a dual phase polymeric delivery composition according to claim 1, (2) maintaining said composition as a liquid; and (3) administering said composition as a liquid to the biological environment, with subsequent gel formation in the biological environment in response to a stimuli.

34. The method according to claim 33 wherein said administration is via parenteral, ocular, topical, inhalation, transdermal, vaginal, buccal, transmucosal, transurethral, rectal, nasal, oral, pulmonary or aural routes.

35. The method according to claim 33 wherein the biological environment is a warm blooded animal.

36. A method for delivering an agent to a biological environment in a controlled manner for a prolonged period of time, comprising the steps of: (1) providing a dual phase polymeric delivery composition according to claim 1, (2) gelling said composition; and (3) administering said composition as a gel to the biological environment.

37. The method according to claim 36 wherein said administration is via parenteral, ocular, topical, inhalation, transdermal, vaginal, buccal, transmucosal, transurethral, rectal, nasal, oral, pulmonary or aural routes.

38. The method according to claim 37 wherein the biological environment is a warm blooded animal.

39. A method for enhancing the stability of a drug during the release from a microparticle delivery system process by providing a dual phase

biodegradable polymeric delivery composition according to claim 1.

L26 ANSWER 54 OF 54 USPATFULL on STN
1998:161995 Methods for treating cancers and pathogen infections using antigen-presenting cells loaded with RNA.
Nair, Smita K., Durham, NC, United States
Boczkowski, David J., Durham, NC, United States
Gilboa, Eli, Durham, NC, United States
Duke University, Durham, NC, United States (U.S. corporation)
US 5853719 19981229
APPLICATION: US 1996-640444 19960430 (8)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A method for producing an RNA-**loaded** antigen presenting cell (APC) that presents on its surface a tumor antigenic epitope encoded by the RNA, wherein the epitope induces T cell proliferation, said method comprising: introducing into an antigen-presenting cell in vitro RNA obtained from a tumor comprising tumor-specific RNA that encodes an antigen that induces T cell proliferation and tumor immunity thereby producing an RNA-**loaded** APC that presents on its surface a tumor antigenic epitope encoded by the RNA, wherein the epitope induces T cell proliferation.

2. The method of claim 1, wherein said APC is a dendritic cell.

3. The method of claim 1, wherein said APC is a **macrophage**.

4. The method of claim 1, wherein said APC is an endothelial cell.

5. The method of claim 1, wherein said APC is an artificially generated APC.

6. The method of claim 1, wherein said RNA comprises poly A+ RNA.

7. The method of claim 1, wherein said RNA comprises cytoplasmic RNA.

8. The method of claim 1, wherein said RNA is tumor-specific RNA.

9. The method of claim 1, wherein the RNA is introduced into the APC by contacting the APC with the RNA in the presence of a cationic lipid.

10. The RNA-**loaded** APC produced by the method of claim 1.

11. The method of claim 1, wherein the RNA is obtained from a melanoma.

12. The method of claim 1, wherein the RNA is obtained from a bladder tumor.

13. The method of claim 1, wherein the tumor-derived RNA is derived from a tumor selected from the group consisting of breast cancer tumors, colon cancer tumors, prostate cancer tumors, and ovarian cancer tumors.

14. The method of claim 1, wherein said RNA is isolated from a cell.

15. The method of claim 1, wherein said RNA is prepared by in vitro amplification and transcription.

16. The method of claim 1, wherein said RNA comprises nuclear RNA.

17. The method of claim 1 wherein said RNA comprises a minigene.

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=> d his

     (FILE 'HOME' ENTERED AT 16:51:29 ON 28 SEP 2006)

     FILE 'USPATFULL' ENTERED AT 16:51:54 ON 28 SEP 2006
                E DREYFUS P A/IN
L1            2 S E4
                E PARRISH ELAINE/IN
L2            2 S E3
L3            0 S L2 NOT L1
                E GARCIA LUIS/IN
L4           27 S E3-E5
L5           25 S L4 NOT L1
L6            0 S L5 AND (MONOCYT? OR MACROPHAG? OR PHAGOCYT?)
                E PELTEKIAN ELISE/IN
L7            3 S E3
L8            1 S L7 NOT L1
                E BARTHOLEYNS JACQUE/IN
L9           23 S E4
L10          21 S L9 NOT L1

     FILE 'WPIDS' ENTERED AT 16:59:22 ON 28 SEP 2006
                E DREYFUS P A/IN
L11           1 S E3
                E PARRISH E/IN
L12           1 S E3
L13           0 S L12 NOT L11
                E GARCIA L/IN
L14          40 S E3
L15           1 S L14 AND (MONOCYT? OR MACROPHAGE OR PHAGOCYT?)
                E PELTEKIAN E/IN
L16           2 S E3
L17           1 S L16 NOT L11

     FILE 'MEDLINE' ENTERED AT 17:02:36 ON 28 SEP 2006
                E DREYFUS P A/AU
L18         133 S E2 OR E3
L19           3 S L18 AND (MONOCYT? OR MACROPHAG? OR PHAGOCYT?)
                E PARRISH E P/AU
L20           9 S E3
                E PELTEKIAN E/AU
L21           7 S E3-E4
L22           6 S L21 NOT (L18 OR L20)

     FILE 'USPATFULL' ENTERED AT 17:15:32 ON 28 SEP 2006
L23       32398 S (MONOCYTE OR MACROPHAGE OR PHAGOCYTE)
L24        3479 S L23 AND (MONOCYTE?/CLM OR MACROPHAG?/CLM OR PHAGOCYT?/CLM)
L25          59 S L24 AND (CARGO/CLM OR LOADED/CLM)
L26          54 S L25 NOT (L1 OR L4 OR L9 OR L7)

=> file wpids
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                 ENTRY    SESSION
FULL ESTIMATED COST                              119.44     230.57

FILE 'WPIDS' ENTERED AT 17:20:34 ON 28 SEP 2006
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FILE LAST UPDATED:          27 SEP 2006      <20060927/UP>
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MOST RECENT DERWENT UPDATE:     200662        <200662/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

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http://www.stn-international.de/stndatabases/details/ipc_reform.html and
http://scientific.thomson.com/media/scpdf/ipcrdwpi.pdf <<<

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    INDEX ENHANCEMENTS PLEASE VISIT:
http://www.stn-international.de/stndatabases/details/dwpi_r.html <<<

=> s (monocyte or macrophage or phagocyte)
          1785 MONOCYTE
          4093 MACROPHAGE
           313 PHAGOCYTE
L27       5538 (MONOCYTE OR MACROPHAGE OR PHAGOCYTE)

=> s l27 and (cargo or loaded)
         16049 CARGO
        184010 LOADED
L28         82 L27 AND (CARGO OR LOADED)

=> s l28 and (CNS or central nervous system)
         14797 CNS
        435397 CENTRAL
         14352 NERVOUS
       2378243 SYSTEM
          8090 CENTRAL NERVOUS SYSTEM
                 (CENTRAL(W)NERVOUS(W)SYSTEM)
L29          3 L28 AND (CNS OR CENTRAL NERVOUS SYSTEM)

=> d l29,bib,1-3

L29  ANSWER 1 OF 3  WPIDS  COPYRIGHT 2006 THE THOMSON CORP on STN
Full Text
AN   2005-332657 [34]   WPIDS
DNC  C2005-228231
TI   New cell line which expresses Thomsen-Friedenreich antigen, polymorphic
     epithelial mucin and glycoprotein, for preparing a pharmaceutical or
     vaccine for the treatment or prevention of cancers and/or tumorous
     diseases.
DC   B04 D16
IN   BAUMEISTER, H; GOLETZ, S; SCHLANGSTEDT, M; SCHOEBER, U
PA   (GLYC-N) GLYCOTOPE GMBH
CYC  109
PI   WO 2005017130   A2 20050224 (200534)* EN   76
        RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE
            LS LU MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
         W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE
            DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG
            KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ
            OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG
            US UZ VC VN YU ZA ZM ZW
     EP 1654353      A2 20060510 (200632)  EN
         R: AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LU MC NL PL
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PT RO SE SI SK TR
ADT WO 2005017130 A2 WO 2004-EP9281 20040818; EP 1654353 A2 EP 2004-764266 20040818, WO 2004-EP9281 20040818
FDT EP 1654353 A2 Based on WO 2005017130
PRAI EP 2003-18576 20030818

L29 ANSWER 2 OF 3 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN
Full Text
AN 2005-075061 [08] WPIDS
DNC C2005-025777
TI Composition for delivering drug to brain for treating **central nervous system** disorders e.g. Parkinson's disease comprises a dispersion of particulate pharmaceutical composition having specific size acceptable by brain cells.
DC A96 B05 B07
IN GENDELMAN, H; KIPP, J; RABINOW, B; KIPP, J E; GENDELMAN, H E; RABINOW, B E
PA (GEND-I) GENDELMAN H; (KIPP-I) KIPP J E; (RABI-I) RABINOW B; (BAXT) BAXTER INT INC
CYC 109
PI WO 2004112747 A2 20041229 (200508)* EN 48
RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
US 2005048002 A1 20050303 (200517)
EP 1663158 A2 20060607 (200638) EN
R: AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LU MC NL PL PT RO SE SI SK TR
ADT WO 2004112747 A2 WO 2004-US18850 20040615; US 2005048002 A1 Provisional US 2003-482096P 20030624, US 2004-868680 20040615; EP 1663158 A2 EP 2004-776540 20040615, WO 2004-US18850 20040615
FDT EP 1663158 A2 Based on WO 2004112747
PRAI US 2003-482096P 20030624; US 2004-868680 20040615

L29 ANSWER 3 OF 3 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN
Full Text
AN 1999-347126 [29] WPIDS
DNN N1999-259569 DNC C1999-102069
TI Diagnosis and treatment of pathologies.
DC B04 D16 S03
IN BARTHOLEYNS, J; CHOKRI, M; DREYFUS, P A; GARCIA, L; PARRISH, E; PELTEKIAN, E
PA (IDMI-N) IDM IMMUNO-DESIGNED MOLECULES; (INRM) INSERM INST NAT SANTE RECH MEDICALE; (BA P A; (GARC-I) GARCIA L; (PARR-I) PARRISH E; (PELT-I) PELTEKIAN E
CYC 83
PI WO 9913054 A2 19990318 (199929)* EN 24
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW
AU 9894410 A 19990329 (199932)
EP 1009806 A2 20000621 (200033) EN
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
JP 2001515713 W 20010925 (200170) 34
US 2002068048 A1 20020606 (200241)
AU 752676 B 20020926 (200268)
US 2005048039 A1 20050303 (200517)

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ADT  WO 9913054 A2 WO 1998-EP5707 19980831; AU 9894410 A AU 1998-94410
     19980831; EP 1009806 A2 EP 1998-947533 19980831, WO 1998-EP5707 19980831;
     JP 2001515713 W WO 1998-EP5707 19980831, JP 2000-510843 19980831; US
     2002068048 A1 US 1997-924830 19970905; AU 752676 B AU 1998-94410 19980831;
     US 2005048039 A1 Div ex US 1997-924830 19970905, US 2004-766929 20040130
FDT  AU 9894410 A Based on WO 9913054; EP 1009806 A2 Based on WO 9913054; JP
     2001515713 W Based on WO 9913054; AU 752676 B Previous Publ. AU 9894410,
     Based on WO 9913054
PRAI US 1997-924830       19970905; US 2004-766929       20040130


=> file medline
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                      20.21     250.78

FILE 'MEDLINE' ENTERED AT 17:21:48 ON 28 SEP 2006

 FILE LAST UPDATED: 27 Sep 2006 (20060927/UP).  FILE COVERS 1950 TO DATE.

 On December 11, 2005, the 2006 MeSH terms were loaded.

 The MEDLINE reload for 2006 is now (26 Feb.) available.  For details
 on the 2006 reload, enter HELP RLOAD at an arrow prompt (=>).
 See also:

    http://www.nlm.nih.gov/mesh/
    http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html
    http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_med_data_changes.html
    http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_2006_MeSH.html

 OLDMEDLINE is covered back to 1950.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2006 vocabulary.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> s (monocyte? or macrophage? or phagocyt?)
         66702 MONOCYTE?
        154165 MACROPHAGE?
         61513 PHAGOCYT?
L30     229855 (MONOCYTE? OR MACROPHAGE? OR PHAGOCYT?)

=> s l30 and (cargo or loaded)
          2033 CARGO
         27837 LOADED
L31       1375 L30 AND (CARGO OR LOADED)

=> s l31 and (CNS or central nervous system)
         49955 CNS
        371988 CENTRAL
        286982 NERVOUS
       1259942 SYSTEM
        126320 CENTRAL NERVOUS SYSTEM
                 (CENTRAL(W)NERVOUS(W)SYSTEM)
L32         15 L31 AND (CNS OR CENTRAL NERVOUS SYSTEM)

=> d l32,ti,1-15

L32  ANSWER 1 OF 15     MEDLINE on STN
```

TI Analysis of lesion development during acute inflammation and remission in a rat model of experimental autoimmune encephalomyelitis by visualization of **macrophage** infiltration, demyelination and blood-brain barrier damage.

L32 ANSWER 2 OF 15 MEDLINE on STN
TI Uptake and presentation of malignant glioma tumor cell lysates by **monocyte**-derived dendritic cells.

L32 ANSWER 3 OF 15 MEDLINE on STN
TI Mannose receptor expression specifically reveals perivascular **macrophages** in normal, injured, and diseased mouse brain.

L32 ANSWER 4 OF 15 MEDLINE on STN
TI Role of peripheral benzodiazepine receptors on secretion of surfactant in guinea pig alveolar type II cells.

L32 ANSWER 5 OF 15 MEDLINE on STN
TI Iron primes hepatic **macrophages** for NF-kappaB activation in alcoholic liver injury.

L32 ANSWER 6 OF 15 MEDLINE on STN
TI Dose and scanning delay using USPIO for **central nervous system macrophage** imaging.

L32 ANSWER 7 OF 15 MEDLINE on STN
TI The cerebral perivascular cells.

L32 ANSWER 8 OF 15 MEDLINE on STN
TI Removal of cobalt-labeled neurons and nerve fibers by microglia from the frog's brain and spinal cord.

L32 ANSWER 9 OF 15 MEDLINE on STN
TI Chromogranin A triggers a phenotypic transformation and the generation of nitric oxide in brain microglial cells.

L32 ANSWER 10 OF 15 MEDLINE on STN
TI Polyomavirus-infected oligodendrocytes and **macrophages** within astrocytes in progressive multifocal leukoencephalopathy (PML).

L32 ANSWER 11 OF 15 MEDLINE on STN
TI Experimental brain injury induces expression of interleukin-1 beta mRNA in the rat brain.

L32 ANSWER 12 OF 15 MEDLINE on STN
TI Distribution of dietary mercury in a dog. Quantitation and localization of total mercury in organs and **central nervous system**.

L32 ANSWER 13 OF 15 MEDLINE on STN
TI Ultrastructural study of **phagocytic** activities of young astrocytes in injured neonatal rat brain following intracerebral injection of colloidal carbon.

L32 ANSWER 14 OF 15 MEDLINE on STN
TI Accumulation of 14C-5,6-dihydroxytryptamine-melanin in intrathecal and subependymal **phagocytes** of the rat **CNS** and possible routes of their elimination from brain.

L32 ANSWER 15 OF 15 MEDLINE on STN
TI [The perinatal neuroglia in hypoxia. An electron- and light microscopical study with addition Golgi's impregnation (author's transl)].
Die perinatale Neuroglia unter besonderer Berucksichtigung der Hypoxie. Eine elektronen- und lichtoptische Untersuchung unter Hinzunahme der

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     Golgi-Impragnation.


=> d his

     (FILE 'HOME' ENTERED AT 16:51:29 ON 28 SEP 2006)

     FILE 'USPATFULL' ENTERED AT 16:51:54 ON 28 SEP 2006
                E DREYFUS P A/IN
L1            2 S E4
                E PARRISH ELAINE/IN
L2            2 S E3
L3            0 S L2 NOT L1
                E GARCIA LUIS/IN
L4           27 S E3-E5
L5           25 S L4 NOT L1
L6            0 S L5 AND (MONOCYT? OR MACROPHAG? OR PHAGOCYT?)
                E PELTEKIAN ELISE/IN
L7            3 S E3
L8            1 S L7 NOT L1
                E BARTHOLEYNS JACQUE/IN
L9           23 S E4
L10          21 S L9 NOT L1

     FILE 'WPIDS' ENTERED AT 16:59:22 ON 28 SEP 2006
                E DREYFUS P A/IN
L11           1 S E3
                E PARRISH E/IN
L12           1 S E3
L13           0 S L12 NOT L11
                E GARCIA L/IN
L14          40 S E3
L15           1 S L14 AND (MONOCYT? OR MACROPHAGE OR PHAGOCYT?)
                E PELTEKIAN E/IN
L16           2 S E3
L17           1 S L16 NOT L11

     FILE 'MEDLINE' ENTERED AT 17:02:36 ON 28 SEP 2006
                E DREYFUS P A/AU
L18         133 S E2 OR E3
L19           3 S L18 AND (MONOCYT? OR MACROPHAG? OR PHAGOCYT?)
                E PARRISH E P/AU
L20           9 S E3
                E PELTEKIAN E/AU
L21           7 S E3-E4
L22           6 S L21 NOT (L18 OR L20)

     FILE 'USPATFULL' ENTERED AT 17:15:32 ON 28 SEP 2006
L23       32398 S (MONOCYTE OR MACROPHAGE OR PHAGOCYTE)
L24        3479 S L23 AND (MONOCYTE?/CLM OR MACROPHAG?/CLM OR PHAGOCYT?/CLM)
L25          59 S L24 AND (CARGO/CLM OR LOADED/CLM)
L26          54 S L25 NOT (L1 OR L4 OR L9 OR L7)

     FILE 'WPIDS' ENTERED AT 17:20:34 ON 28 SEP 2006
L27        5538 S (MONOCYTE OR MACROPHAGE OR PHAGOCYTE)
L28          82 S L27 AND (CARGO OR LOADED)
L29           3 S L28 AND (CNS OR CENTRAL NERVOUS SYSTEM)

     FILE 'MEDLINE' ENTERED AT 17:21:48 ON 28 SEP 2006
L30      229855 S (MONOCYTE? OR MACROPHAGE? OR PHAGOCYT?)
L31        1375 S L30 AND (CARGO OR LOADED)
L32          15 S L31 AND (CNS OR CENTRAL NERVOUS SYSTEM)
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=> log off
ALL L# QUERIES AND ANSWER SETS ARE DELETED AT LOGOFF
LOGOFF? (Y)/N/HOLD:y
STN INTERNATIONAL LOGOFF AT 17:23:34 ON 28 SEP 2006
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